● PERSPECTIVE

The neuroprotective effects of the anti-diabetic drug linagliptin against Aβ-induced neurotoxicity

Impaired insulin signaling in Alzheimer's disease (AD) brains: The insulin signaling pathway is a fundamental physiological mechanism that presents in nearly all vertebrate cells. However, sometimes cells stop responding properly to insulin stimulation. This condition is known as insulin resistance, which is a hallmark of two very common conditions, metabolic syndrome and type 2 diabetes (T2D). Interestingly, there is also increasing evidence that insulin resistance itself may affect central nervous system (CNS) functions. Particularly, impaired insulin signaling in the brain has been linked to AD, the most common type of dementia caused by cerebral accumulation of the amyloid β (Aβ). Actually, increasing evidence suggests defective brain insulin signaling may directly play a key role in AD pathogenesis. Brain insulin resistance was firstly proposed to implicate reduced brain metabolism in neurodegeneration by Hoyer et al. (1994). Although the detailed mechanism of the brain insulin resistance is uncertain, a serial studies reported significantly decreased neuronal insulin signaling in the cortex and hippocampus of AD cases (Bedse et al., 2015). Consistent with these observations, T2D is identified epidemiologically as a major risk factor for AD, suggesting a possibility that defective insulin signaling may account for AD pathogenesis. Actually, insulin and its receptors are widely expressed in neurons and glial cells throughout the brain. This implicates that insulin signaling may contribute to control of cognition and neuronal function in brains. In fact, AD often shares some common pathophysiologic hallmarks with T2D, such as impaired glucose metabolism and glycogen synthase kinase-3β (GSK3β) hyperactivation. In addition, Aβ peptide has been reported to inhibit synaptic insulin sensitivity directly in cultured neurons, which may impair synaptic functions associated with pathogenesis of AD (Heras-Sandoval et al., 2012). Moreover, patients with AD show significantly reduced expression of insulin receptors and insulin receptor substrate (IRS) which corrects to the severity of cognitive impairment (De Felice et al., 2014). All these findings suggest that insulin resistance is a common feature in both AD and T2D.

Glucagon-like peptide-1 and insulin signaling: Incretins are gut hormones that work to increase insulin secretion and action. There are two main incretin hormones in humans, including glucagon-like peptide (GLP) and glucose-dependent insulinotropic polypeptide (GIP). However, subsequent studies revealed that the GLP, particularly GLP-1, is the most potent incretin that regulates insulin secretion in human bodies. The pharmacological action of GLP-1 is to stimulate pancreatic β cells to secrete more insulin in response to blood glucose. Thus, GLP-1 increases insulin secretion but do it in a way by glucose dependent. Unlike traditional diabetic drugs may cause side effects of hypoglycemia, GLP-1 has an advantage only to cause insulin secretion when blood sugar levels rise and stay high. As a result, GLP-related therapies are now emerging as safe and promising therapies for T2D and its associated complications. For example, liraglutide is a synthetic GLP-1 mimic and more effective than native GLP-1 because of resistance to degradation by dipeptidyl peptidase 4 (DPP-4), the major protease rapidly cleaves and inactivates endogenous incretin peptides. In addition, another class of drugs are the specific inhibitors of DPP-4, which prolongs the action of the native GLP-1 by preventing their breakdown. Unlike the GLP-1 agents must be injected, and the main advantage of DPP-4 inhibitors is that they can be taken orally. Thus, DPP-4 inhibitors are the most widely used incretin-based therapy for the treatment of T2D.

Significance of GLP-1 on AD brain: Interestingly, GLP-1 also has very similar neuroprotective properties to insulin, and has been shown to protect against AD pathological processes. Similar to insulin, GLP-1 is produced in the brain mediating many neuronal functions, including neuroprotection, improvement of learning and memory ability, and potentiation of insulin signaling (Holscher, 2014). This indicates GLP-1 may display the potential to serve as therapeutic or preventive strategies against diabetes-related AD. As DPP-4 inhibitors can effectively increase GLP-1 levels, they may also exert protective effects against AD-related neurodegeneration. It is known that the proglucagon gene encodes GLP-1 peptides, which is located on the long arm of human chromosome 2 with the entire coding sequence within exon 4. In past years, GLP-1 peptide is thought to be mainly expressed in the pancreas α cells and intestine L-cells. However, mammalian GLP-1 gene is now known to be actively transcribed in brain neurons (Bassil et al., 2014). This indicates that GLP-1 is also a physiologic regulator in CNS. Accordingly, GLP-1 signaling is known to modulate many neuronal functions in the brain; therefore, GLP-1 signaling has demonstrated the potential to serve as therapeutic or preventive strategies against diabetes-related AD (Xiong et al., 2013).

Restoring Aβ-impaired neuronal insulin signaling by linagliptin: Because DPP-4 inhibitor can effectively increase GLP-1 levels, it is conceivable that DPP-4 inhibitor may also improve brain insulin action and exert protective effects against AD-impaired insulin signaling. Particularly, linagliptin gas recently been reported to be a putative neuroprotective agent. It is known that linagliptin demonstrates greater inhibitory effects than other common DPP-4 inhibitors such as alogliptin, saxagliptin, sitagliptin or vildagliptin (Thomas et al., 2008). Moreover, linagliptin also shows the ability to improve insulin secretory dysfunction and sensitivity in animal studies. This implies that linagliptin may have beneficial effects on impaired insulin signaling in neuronal cells. In this regard, we recently provided evidence that linagliptin can protect neuronal cells against Aβ-induced neurotoxicity. The mechanism is most likely caused by the blockade of DPP-4, which makes GLP-1 levels rise and sudsequently increases insulin release as well as restores insulin signals (Kornelius et al., 2015). In accordance with these findings, we also found that the activity of 5′ AMP-activated protein kinase (AMPK) could be reduced during the incubation of cells with Aβ, and this inhibition was prevented by linagliptin co-treatment. Moreover, we also observed that linagliptin protects mitochondrial function and suppresses intracellular reactive oxygen species (ROS) accumulation depending on AMPK and insulin signaling pathways. These results indicated linagliptin can trigger AMPK and its downstream target Sirt1, resulting in restoring insulin downstream signaling activity and reducing oxidative stress (**Figure 1**). Considering the important roles of the Aβ-induced oxidative stress in AD pathogenesis, these observations unveil a potential neuroprotective mechanism by linagliptin through suppressing oxidative damage and preserving mitochondria function *via* restoration of neuronal insulin signaling.

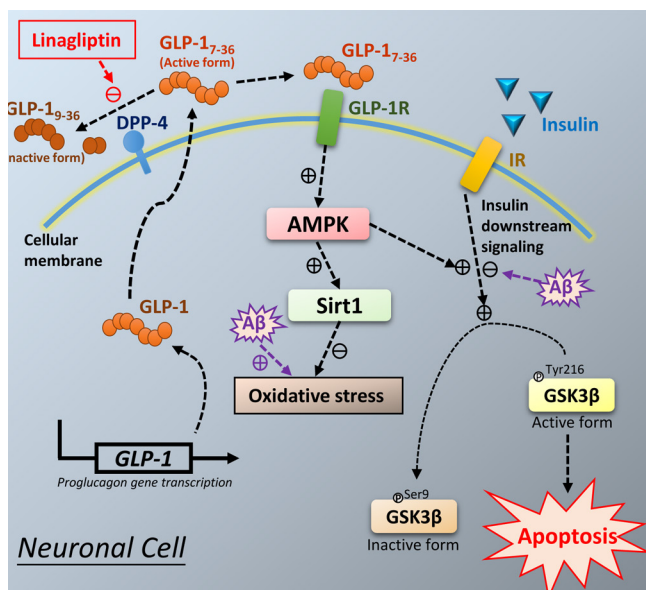Stimulation of brain GLP-1 signaling as a novel therapeutic

Figure 1 A proposed scheme for the protective effects of linagliptin against Aβ-induced neuronal insulin signaling blockade.
GLP-1 is synthesized and secreted by neuronal cells. Thus, stimulation of GLP-1 receptor (GLP-1R) and subsequently activate downstream AMPK/Sirt1 pathway which protects mitochondrial function and suppresses intracellular ROS accumulation. However, the DPP-4 enzyme rapidly inactivates GLP-1, resulting in downregulation of GLP-1 downstream effects. On the contrary, therapeutic candidates against DPP-4 like linagliptin may display neuroprotective effects by rescuing suppressed GLP-1 signaling, which can work against neuronal insulin signaling blockade thereby attenuating Aβ-induced neuronal cell death. Aβ: Amyloid β; AMPK: 5′ AMP-activated protein kinase; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; GSK3β: glycogen synthase kinase-3β; IR: insulin receptor; ROS: reactive oxygen species; Ser9: phospho-GSK-3β; Sirt1: sirtuin 1; Tyr216: p-GSK-3β/β antibody.

approach in AD: Recently, Kosaraju et al. (2014) reported that inhibition of DPP-4 ameliorates streptozotocin-induced memory loss and neurodegeneration, indicating the possibility of using of these agents for treating T2D-associated diseases such as AD. Their results revealed a significant improvement in a dose-dependent attenuation of Aβ production, tau hyperphosphorylation and cognitive deficits by upregulation of GLP-1 signaling. This suggests that DPP-4 inhibitors may demonstrate a unique mechanism for Aβ-related pathology observed in AD. However, a previous study has demonstrated that compared to GLP-1 a peptides, linagliptin does not pass through the blood-brain barrier easily. Because linagliptin has been suggested to have direct neuroprotective effects, we postulate that linagliptin treatment may locally increase levels of brain GLP-1 and confers its neuroprotection. This is further supported by the fact that linagliptin-mediated neuroprotection occurs directly at the neuronal level because the brain expression of GLP-1 receptors is exclusively in neurons (Darsalia et al., 2013). However, further studies are necessary to confirm the neuroprotective effect of linagliptin in AD patients.

Conclusions: AD is the most common form of neurodegenerative dementia. Although there are currently some drugs licensed for the symptom improvements, no drug treatments can provide a cure for AD. Recent reports demonstrate shared clinical and pathophysiological traits between AD and T2D, suggesting that AD may be a brain-specific form of diabetes. Although the underlying mechanism remains largely unknown, now the evidence for it has become very significant. Actually, de la Monte

et al. have proposed a connection between increased insulin resistance in the brain with AD and termed it as "type 3 diabetes" (Steen et al., 2005), indicating that insulin-based therapies may be useful in the treatment of AD. Accordingly, several drugs have been developed to treat T2D that resensitize insulin signaling and may be of use to prevent neurodegenerative processes such as AD. In this regard, we suggest that Aβ may disrupt normal brain insulin signaling, similar to what happens in peripheral tissue in T2D. This suggests that incretin-based strategies may have emerged as novel successful therapies for AD, either using GLP-1 agonists or DPP-4 inhibitors such as linagliptin.

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