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LETTER TO THE EDITOR

Linagliptin—Role in the Reversal of Aβ-Mediated Impairment of Insulin Signaling and Reduced Neurotoxicity in AD Pathogenesis: Some Considerations

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Dipeptidyl peptidase-4 (DPP-4) is responsible for degradation of incretin; premature loss of incretin can lead to erratic cellular signaling and decreased insulin secretion [1]. Linagliptin is a potent DPP-4 inhibitor and thereby can prevent the rapid metabolism of incretin so that the physiological role of incretin can be sustained [2]. The major incretin hormone, glucagon peptide-like 1 (GLP-1), is also produced in the brain in addition to the gut. Therefore, modulation of incretin signaling via effective blockade of DPP-4 by linagliptin may have a role to play in therapeutic options to treat diabetes-related Alzheimer's disease (AD) [3].

Recently, Kornelius et al. (2015) have systematically investigated the possible role of linagliptin in key mechanisms pertaining to the insulin signaling and amyloid β-peptide (Aβ)-related cytotoxicity using *in vitro* systems and well-planned experimental protocols with proper controls [4]. The impaired insulin signaling and Aβ-related toxic manifestations are part of AD pathogenesis. The findings of this extensive work unambiguously suggested that linagliptin can not only reverse impairment of insulin signaling but also protect against neurotoxicity caused by Aβ [4]. Earlier, the work of Kosaraju et al. has established the potential role DPPIV inhibitors may play as disease-modifying agents for the treatment of AD [5,6]. Both saxagliptin and vildagliptin showed similar pharmacological and pharmacodynamic effects in the streptozotocin-induced rat model of AD. Despite differences in the oral doses and study regimens of the two DPP-4 inhibitors (saxagliptin—daily dosing at 0.25, 0.5, and 1 mg/kg for 60 days; vildagliptin—daily dosing at 2.5, 5 and 10 mg/kg for 30 days), the end result of a considerable attenuation of Aβ, modulation of tau phosphorylation for an effective clearance, and significant impact on inflammatory markers were comparable. Furthermore, both saxagliptin and vildagliptin showed an improvement in the hippocampal GLP-1 production and reversal of the behavioral deficits [5,6].

The human translation of the *in vitro* and *in vivo* findings of the possible role of GLP-1 in the brain for a potential reversal of the AD pathogenesis is being clinically investigated in two different Phase 2 AD patient trials involving exendin-4 [7] and liraglutide [8]. The study of exendin-4 in patients with AD has been designed with specific efficacy-related objectives of obtaining (a) behavioral and cognitive scores; (b) relative changes in the brain MRI scans with regard to functionality and structural architecture; (c) changes on the AD-related biomarkers including Aβ levels and Tau modulation in the cerebrospinal fluid; and (d) clinical and performance scores as measured by clinical dementia rating and AD assessment scale [7]. The study of liraglutide in patients with mild AD has the following efficacy-related objectives: (a) to measure the change in the cerebral glucose metabolic rate with proper stratification of the patients with AD and (b) to obtain data on changes related to MRI evaluation, AD biomarkers, and CSF analysis [8].

The intent of this report is to provide some thoughts and perspectives on the *in vivo* translatability of such *in vitro* findings given the reported pharmacokinetic disposition of linagliptin in relation to other DPP-4 inhibitors such as saxagliptin and vildagliptin.

Linagliptin is a good substrate for P-glycoprotein (Pgp) [9] which not only limits the oral absorption but may also have a significant role to play in effluxing linagliptin from the brain and therefore rendering negligible entry of linagliptin into the brain. To underscore this view point, a rat tissue distribution study showed that [^{14}C]linagliptin was not present in either the brain or the cerebral spinal fluid; however, [^{14}C]linagliptin was extensively distributed across all other organs and tissues in the rats [10]. Therefore, the key question that remains at large is: would

linagliptin penetrate blood–brain barrier (BBB) to promote local action on restoring incretin levels in the brain tissue to support the *in vivo* translatability of the present work.

To address this important question, the following arguments are proposed: (a) The physiological consequence of AD leads to reduced BBB resistance resulting in a lower efflux of Aβ and greater influx of Aβ into the brain [11]; however, this may be a blessing in disguise because it may provide an opportunity for linagliptin to penetrate BBB and reverse the Aβ-mediated pathophysiology by favorably modulating the incretin levels via blocking DPP-4 enzyme localized in the brain and as well activate AMPK in the neuronal cells to reduce the cytotoxic potential of Aβ and rendering neuroprotective properties; (b) based on the mass balance profile in animals and humans, biliary excretion of both intact linagliptin and metabolites appears to be a major route of elimination [10]. Although confirmation of an effective hepatobiliary recycling pathway for linagliptin has not been established [10], it is quite possible that such a pathway can increase the gut residence of linagliptin and in turn may aid in its sustained pharmacodynamic effect via modulating gut incretin hormones. Perhaps the restoration of gut incretin levels by linagliptin may also indirectly help in the regulation of brain incretin hormones due to the overall establishment of glucose homeostasis, although this remains somewhat speculative in nature; (c) interestingly relative to saxagliptin and vildagliptin, the pharmacokinetic disposition in humans of linagliptin is remarkably different [12,13]. As summarized in recent articles, saxagliptin showed the highest metabolic conversion (hepatic metabolism) of approximately 51% as compared to vildagliptin (10%) in humans [12,13]. The hepatic metabolism of linagliptin was almost negligible (2%), suggesting that a greater fraction of linagliptin escaped hepatic metabolism. Despite a greater plasma protein binding reported for linagliptin (approximately >75%) as compared to either saxagliptin (<10%) or vildagliptin (9%), linagliptin appeared to have extensive tissue distribution in humans [13].

In summary, while examination and confirmation of mechanisms and processes at cellular levels by *in vitro* tools and/or preclinical models are very vital for the probing and understanding of the drug pharmacotherapy, it may also be important to consider translatability of such findings under *in vivo* conditions. The scrutiny of the *in vivo* data in the streptozotocin-induced rat model of AD for saxagliptin and vildagliptin overwhelmingly supports the role of linagliptin in attenuating the AD-related pathophysiology. The differential pharmacokinetic disposition of linagliptin in relation to either saxagliptin or vildagliptin should also favor in its role as a potential disease-modifying drug in AD.

Conflict of Interest

The author declares no conflict of interest.

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