Role of liraglutide in Alzheimer’s disease pathology

Maria Vargas-Soria†, Maria Jose Carranza-Naval†,2†, Angel del Marco* and Monica Garcia-Alloza*

Abstract

Background: The described relationship between Alzheimer’s disease (AD) and type 2 diabetes (T2D) and the fact that AD has no successful treatment has led to the study of antidiabetic drugs that may limit or slow down AD pathology.

Main body: Although T2D treatment has evident limitations, options are increasing including glucagon-like peptide 1 analogs. Among these, liraglutide (LRGT) is commonly used by T2D patients to improve β cell function and suppress glucagon to restore normoglycaemia. Interestingly, LRGT also counterbalances altered brain metabolism and has anti-inflammatory properties. Previous studies have reported its capacity to reduce AD pathology, including amyloid production and deposition, tau hyperphosphorylation, or neuronal and synaptic loss in animal models of AD, accompanied by cognitive improvement. Given the beneficial effects of LRGT at central level, studies in patients have been carried out, showing modest beneficial effects. At present, the ELAD trial (Evaluating Liraglutide in Alzheimer’s Disease NCT01843075) is an ongoing phase IIb study in patients with mild AD. In this minireview, we resume the outcomes of LRGT treatment in preclinical models of AD as well as the available results in patients up to date.

Conclusion: The effects of LRGT on animal models show significant benefits in AD pathology and cognitive impairment. While studies in patients are limited, ongoing clinical trials will probably provide more definitive conclusions on the role of LRGT in AD patients.

Keywords: Liraglutide, Alzheimer’s disease, Amyloid, Tau, Inflammation, Cognition
pathologies, inflammation, and neuronal damage are observed in animal models, supporting further studies in patients.

**Main text**

**Preclinical studies**

Glucagon-like peptide 1 (GLP-1) is implicated in the control of glycemia and metabolic homeostasis, both in the periphery and the central nervous system [7, 8]. Due to the importance of GLP-1 signaling on cognitive function [9] and the relationship between AD and T2D [10], GLP-1 analogs, and LRGT specifically, may provide a relevant venue to ameliorate AD pathology [11]. Previous studies have shown some controversial outcomes in AD models. Whereas brain weight [12, 13], hippocampal insulin [13–16], cortical glucose levels or brain GLUT1 and GLUT4 [13] do not seem to be affected, LRGT treatment increases GLP1-receptors in the hippocampus of AD mice [15–17]. Similarly, LRGT also increases insulin receptor levels in a primate model of AD [14], although no differences have been observed in AD mice [18]. LRGT ameliorates insulin resistance in the hippocampus by reducing phosphorylated insulin receptor levels [19, 20] and insulin receptor substrate-1 [19, 20]. Interestingly, insulin degrading enzyme, that is reduced in AD preclinical models and a feasible underlying mechanism for AD and T2D [21, 22], is preserved or increased in the cortex and hippocampus from AD mice after LRGT treatment [18, 20].

Autopsy cohort studies have revealed a limited role of T2D on classical AD neuropathological features (amyloid (Aβ) plaques and tau tangles) [4]. However, studies in animals show an overall improvement after different administration protocols [12, 13, 23, 24], including prophylactic [23] and long-term treatments [23, 25–27]. Whereas some studies have reported no effects on amyloid pathology [28], the majority of the results show that LRGT dramatically reduces Aβ plaque size [29], number [19, 29], and burden [18, 23, 30–32]. LRGT also decreases Aβ aggregates [30] and restores increased levels of β-secretase 1 and presenilin 1 [17] in the brain from an AD mice, once Aβ pathology is fully established (Fig. 1). Moreover, positive effects have also been observed when LRGT is administered before Aβ plaques deposit [23]. In addition, LRGT limits tau hyperphosphorylation by modulating the activity of ERK and JNK in 3xTgAD [12, 13], APP/PS1 [29], and hTauP301L mice [33]. Likewise, LRGT reduces hippocampal tau phosphorylation by modulating Akt and GSK-3β [15], and in hyperhomocysteinemic rats, tau hyperphosphorylation is reduced through the activation of PP2Ac [17]. Likewise, LRGT neuroprotection is mediated by a reduction of neurofilament phosphorylation in 3xTgAD animals [12]. LRGT also improves synaptic plasticity [18, 34], density [14], structure [15, 27], and synopsis number [35], increasing synaptophysin and PSD-95 levels in AD mice [23, 30, 35] together with increased long-term potentiation and paired-pulse facilitation [18, 30, 34, 35]. NMDA synapse-associated proteins are restored by LRGT in the hippocampus from hyperhomocysteinemic rats [17], and cAMP/PKA pathway is also improved [14, 34]. Additionally, LRGT not only attenuates neural loss and degeneration, but it also increases neurogenesis in the cortex [18, 23, 26, 35] and the subventricular zone [31, 32], reduces the number of degenerating cells in the cortex and hippocampus [12], and increases cell proliferation in the dentate gyrus of AD animals [26]. Inflammation is also a major feature in AD and previous studies show

![Fig. 1 Schematic effects of liraglutide in the brain with AD pathology](image-url)
that LRGT reduces microgliosis and astrocytosis in the cortex [19, 23, 30, 35] and hippocampus [29, 31, 32]. Besides, LRGT limits pro-inflammatory cytokines, including TNF-α, IL-1β, or IL-10 [13, 24]. In line with these observations, LRGT also decreases brain oxidative stress, by reducing glucose-6-phosphate dehydrogenase activity, the formation of cortical carbonyl groups, nitrite and 8-hydroxy-2′-deoxyguanosine in 3xTgAD mice [13]. Similarly, oxidative phosphorylation of cortical astrocytes is reduced in 5xFAD mice [27] (Fig. 1).

The positive effects of LRGT on AD-like pathology support the beneficial role of LRGT on learning and memory in most of the studies. In this sense, spatial working memory improves after LRGT treatment [12, 15, 17, 18, 24], and LRGT also restores episodic memory in AD models [14, 18, 23] (Fig. 1). In line with these observations, contextual fear conditioning [14], active-avoidance T-maze task [25], or clasp behavior [33] are also improved by LRGT, while locomotor activity does not seem affected [12, 17, 23].

Studies in AD patients

The above described outcomes in preclinical models of AD have set the basis to further assess LRGT in patients. Whereas other antidiabetic drugs, including GLP-1 analogs or dipeptidyl peptidase 4 inhibitors, have been part of preceding or ongoing clinical trials, studies with LRGT specifically are still limited. Previous meta-analysis has shown a pro-cognitive class effect of antidiabetic agents in AD/mild cognitive impairment, although the actual beneficial effects with LRGT are limited [36]. LRGT administration to individuals with subjective cognitive complaints, at risk for AD, improves intrinsic connectivity within brain areas. While this did not translate into cognitive differences between study groups after 12 weeks of treatment [37], other studies have shown that treatment with LRGT to AD patients for 6 months raises blood-brain glucose transfer capacity, restoring glucose transport [38], as an initial requirement to improve brain alterations. Gejl et al. [39] (ClinicalTrials.gov NCT01469351) have also reported that treatment with LRGT to AD patients for 6 months prevents cerebral metabolic rate of glucose consumption decline, as an indicator of cognitive impairment, synaptic dysfunction, and disease evolution. Whereas Aβ load or cognition do not seem to be affected, the authors state the study was underpowered. Another study with pre- or early diabetes patients has recently shown that LRGT improves short-term memory and memory composite in treated patients [40].

The ELAD trial is presently ongoing and the main objectives include evaluation of glucose metabolic consumption in cortical regions and cognition, MRI changes, microglial activation, and amyloid or tau changes [41], and the latest results will be published shortly.

Conclusions

Preclinical studies show beneficial effects of LRGT on AD pathological features and cognition. While the studies in patients have only shown moderate positive effects, the ongoing ELAD trial may provide relevant insights on the actual role of LRGT at central level and open new venues of treatment for AD patients.

Abbreviations

Aβ: Amyloid-β; AD: Alzheimer’s disease; T2D: Type 2 diabetes; GLP-1: Glucagon-like peptide 1; LRGT: Liraglutide

Acknowledgements

Not applicable.

Authors’ contributions

MVS and MJCN drafted the manuscript. ADM and MGA drafted parts of the manuscript and revised and completed the manuscript. The authors read and approved the final manuscript.

Funding

MG-A: Programa Estatal de I+D+I orientada a los Retos de la Sociedad (BFU2016-75038-R), financed by the Agencia Estatal de Investigación (AEI) and the Fondo Europeo de Desarrollo Regional (FEDER), Ministerio de Ciencia, Innovación y Universidades. Explora Ciencia. Ministerio de Ciencia, Innovación y Universidades (BFU2017-91910-EXP). Subvención para la financiación de la investigación y la innovación biomédica y en ciencias de la salud en el marco de la iniciativa territorial integrada 2014-2020 para la provincia de Cádiz. Consejería de Salud. Junta de Andalucía. Unión Europea, financed by the Fondo de Desarrollo Regional (FEDER) (PH-0008-2017).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1Division of Physiology, School of Medicine, Instituto de Investigacion Biomédica de Cadiz (INIBICA), Universidad de Cadiz, Edificio Andres Segovia, C/Dr. Maranon 3, 3er piso, Cadiz, Spain. 2Salus Infirmorum-Universidad de Cadiz, Cadiz, Spain. 3Division of Physiology, School of Medicine, Instituto de Investigacion Biomédica de Cadiz (INIBICA), Universidad de Cadiz, Edificio Andres Segovia, C/Dr. Maranon 3, 3er piso, Cadiz, Spain. 4Division of Physiology, School of Medicine, Instituto de Investigacion Biomédica de Cadiz (INIBICA), Universidad de Cadiz, Edificio Andres Segovia, C/Dr. Maranon 3, 3er piso, Cadiz, Spain.

Received: 21 May 2021 Accepted: 31 May 2021

Published online: 12 June 2021

References

1. Sims-Robinson C, Kim B, Rosko A, Feldman EL. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol. 2010;6(10):551–9. https://doi.org/10.1038/nrneurol.2010.130.

2. Ryu JC, Zimmer ER, Rosa-Neto P, Yoon SO. Consequences of metabolic disruption in Alzheimer’s disease pathology. Neurotherapeutics. 2019;16(3):600–10. https://doi.org/10.1007/s13311-019-00755-y.

3. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease pathology. Neurotherapeutics. 2019;16(3):600–10. https://doi.org/10.1007/s13311-019-00755-y.
liraglutide improves water maze learning and memory performance while reduces hyperphosphorylation of tau and neurofilaments in APP/PS1/Tau triple transgenic mice. Neurochem Res. 2017;42(8):2325–35. https://doi.org/10.1007/s11064-017-2550-8.

15. Duarte AI, Candeias E, Alves IN, Mena D, Silva DF, Machado NJ, et al. Liraglutide and its neuroprotective properties focus on possible biochemical mechanisms in Alzheimer’s disease and cerebral ischemic events. Int J Mol Sci. 2019;20(5).

16. Qi L, Chen Z, Wang Y, Liu X, Liu X, Ke L, et al. Subcutaneous liraglutide and the risk of Alzheimer’s disease: a nationwide population-based study. PLoS One. 2019;14(11):e0220795. https://doi.org/10.1371/journal.pone.0220795.

17. Timper K, Del Rio-Martin A, Cremer AL, Bremser S, Alber J, Giavalisco P, et al. Alzheimer’s Research & Therapy 2019;21:99. https://doi.org/10.1186/s13075-019-1073-7.

18. McLean PL, Paladugu L, Gharaibeh A, Kolli N, Learman C, Hall TC, et al. The GLP-1 receptor agonist liraglutide prevents degenerative processes in a mouse model of Alzheimer’s disease. Mol Metab. 2021;47:101180. https://doi.org/10.1016/j.molmet.2021.101180.

19. Hansen HH, Fabricius K, Bartholf P, Niehoff ML, Morley J, Jelsing J, et al. The GLP-1 receptor agonist liraglutide improves memory function and increases hippocampal CA1 neuronal numbers in a preclinical accelerated mouse model of Alzheimer’s disease. J Alzheimers Dis. 2015;46(4):877–88. https://doi.org/10.3233/JAD-143090.

20. Pathrasarathy V, Holscher C. Chronic treatment with the GLP1 analogue liraglutide increases cell proliferation and differentiation into neurons in an AD mouse model. PLoS One. 2013;8(3):e58784. https://doi.org/10.1371/journal.pone.0058784.

21. Zheng J, Liu Y, Shi X, Li R, Li Q, Wu L, Pan X, et al. GLP-1 improves the supportive ability of astrocytes to neurons by promoting aerobic glycolysis in Alzheimer’s disease. Mol Metab. 2021;47:101180. https://doi.org/10.1016/j.molmet.2021.101180.

22. Holscher C. The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-beta plaque and glial signalling in a mouse model of Alzheimer’s disease. Neurobiol Aging. 2019;71:246–50. https://doi.org/10.1016/j.neurobiolaging.2018.12.002.

23. McLean PL, Paladugu L, Holscher C, Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer’s disease. Neuropharmacology. 2014;86:241–58. https://doi.org/10.1016/j.neuropharm.2014.07.015.

24. Cao B, Rosenblat JD, Bredtke E, Park C, Lee Y, Musial N, et al. Comparative efficacy and acceptability of antidiabetic agents for Alzheimer’s disease and mild cognitive impairment: a systematic review and network meta-analysis. Diabetes Obes Metab. 2018;20(10):2467–71. https://doi.org/10.1111/dom.13373.

25. Watson KT, Wroolie TE, Tong G, Roland-Ross LC, Frangou S, Singh M, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer’s disease: concepts and confounders. Nat Rev Neurol. 2018;14(3):168–81. https://doi.org/10.1038/nrneurol.2017.185.

26. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018;14(10):591–604. https://doi.org/10.1038/s41574-018-0048-7.

27. Wang KC, Woung LC, Tsai MT, Liu CC, Su YH, Li CY. Risk of Alzheimer’s disease in relation to diabetes: a population-based cohort study. Neuroepidemiology. 2012;38(6):237–44. https://doi.org/10.1159/000337428.

28. Huang CC, Chung CM, Leu HB, Lin LY, Chu CI, Hsu CY, et al. Diabetes mellitus and the risk of Alzheimer’s disease: a nationwide population-based study. PLoS One. 2014;9(11):e87095. https://doi.org/10.1371/journal.pone.0087095.

29. Tiemens K, Del Rio-Martin A, Cremers AL, Bremser S, Alber J, Giavalisco P, et al. Alzheimer’s Research & Therapy 2019;20:37. https://doi.org/10.1186/s13075-019-1076-4.

30. Wang KC, Woung LC, Tsai MT, Liu CC, Su YH, Li CY. Risk of Alzheimer’s disease in relation to diabetes: a population-based cohort study. Neuroepidemiology. 2012;38(6):237–44. https://doi.org/10.1159/000337428.
disease. Behav Brain Res. 2019;356:271–8. https://doi.org/10.1016/j.bbr.2018.08.006.
38. Gejl M, Brock B, Egebjerg L, Vang K, Rungeby J, Gjedde A. Blood-brain glucose transfer in Alzheimer’s disease: effect of GLP-1 analog treatment. Sci Rep. 2017;7(1):17490. https://doi.org/10.1038/s41598-017-17718-y.
39. Gejl M, Gjedde A, Egebjerg L, Moller A, Hansen SB, Vang K, et al. In Alzheimer’s disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci. 2016;8:108.
40. Vadini F, Simeone PG, Boccatonda A, Guagnano MT, Liani R, Tripaldi R, et al. Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study. Int J Obes. 2020;44(6):1254–63. https://doi.org/10.1038/s41366-020-0535-5.
41. Femminella GD, Frangou E, Love SB, Busza G, Holmes C, Ritchie C, et al. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer’s disease: study protocol for a randomised controlled trial (ELAD study). Trials. 2019;20(1):191. https://doi.org/10.1186/s13063-019-3259-x.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.