Abstract: Alzheimer’s disease (AD), characterized by the aggregation of amyloid-β (Aβ) protein and neuroinflammation, is the most common neurodegenerative disease globally. Previous studies have reported that some AD patients show impaired glucose utilization in brain, leading to cognitive decline. Recently, diabetes-induced dementia has been called “type 3 diabetes”, based on features in common with those of type 2 diabetes and the progression of AD. Impaired glucose uptake and insulin resistance in the brain are important issues in type 3 diabetes, because these problems ultimately aggravate memory dysfunction in the brain. Glucagon-like peptide 1 (GLP-1) has been known to act as a critical controller of the glucose metabolism. Several studies have demonstrated that GLP-1 alleviates learning and memory dysfunction by enhancing the regulation of glucose in the AD brain. However, the specific actions of GLP-1 in the AD brain are not fully understood. Here, we review evidences related to the role of GLP-1 in type 3 diabetes.

Keywords: glucagon like peptide 1 (GLP-1); type 3 diabetes; diabetes-induced dementia; Alzheimer’s disease (AD); insulin resistance; Amyloid beta (Aβ)

1. Introduction

Alzheimer’s disease (AD) as an age-related neurodegenerative disorder is not well understood in terms of etiology, even though it was first described over 100 years ago [1]. AD is characterized by extracellular accumulation of aggregated amyloid-β (Aβ) protein, intracellular accumulation of hyper-phosphorylated tau protein, neuroinflammation, and a reduction in cerebral glucose consumption [2]. Recent studies have demonstrated that AD has a pathophysiological relationship with type 2 diabetes mellitus (T2DM), in that both involve impairment of insulin signaling and glucose metabolism [3]. Epidemiological studies have indicated that T2DM increases the risk of AD [4,5]. The brain has been known to regulate body energy and control food intake and body weight [6,7]. Additionally, the brain consumes glucose at a high rate, and uses it for propagation of action potentials and maintenance of the membrane potentials required for neuronal transmission [8,9]. AD patients show decreased glucose utilization in brain areas that are directly related to cognitive functions, including the hippocampus and cerebral cortex [10]. According to several studies, the deregulation of glucose metabolism in AD can be controlled by the administration of a hormone known as a potent regulator of glucose homeostasis [11] and of food intake [12], glucagon-like peptide 1 (GLP-1) [13]. The fact that administration of this peptide improves cognitive decline in patients with AD, as well as in AD mouse model [14,15] suggests that deregulation of glucose in the brain is a crucial issue in the onset and progression of AD [4,5,16–18]. Here, we review recent evidence concerning the role of GLP-1 in diabetes-induced dementia. We highlight the importance of GLP-1 in the onset and progression of diabetic AD, sometimes referred to as type 3 diabetes.
2. Diabetes Induced Dementia as the Type 3 Diabetes

Recent studies have demonstrated that patients with T2DM and metabolic syndrome have elevated risk for vascular dementia and AD \[19,20\]. Other studies have reported aberrant cerebral insulin homeostasis, which is called insulin resistance, in AD patients \[21,22\]. In the CNS, insulin is synthesized in neurons such as pyramidal and granule cells in the cerebral cortex and hippocampus \[23,24\]. Pancreatic insulin transported in small amounts across the blood–brain barrier (BBB) could also influence brain function \[25,26\]. Insulin growth factor-1 (IGF-1) and its receptor (IGF-1R) can be observed in the brain and have been related to the control of neurogenesis and synaptogenesis \[27,28\]. Deregulation of brain insulin signaling and IGF-1 signaling affects insulin resistance, energy metabolism, and lipid metabolism and results in pathological changes in the central nervous system (CNS) \[29–32\]. According to several studies, insulin and IGF-1 resistance can be detected in the brains of AD patients \[29\], but the relationship between insulin resistance and brain dysfunction remains unclear \[33\]. Recently, the relationship between brain insulin/IGF-1 signaling impairment and AD has been dubbed type 3 diabetes \[34\]. Further study of the mechanisms involved in the onset and progression of type 3 diabetes is necessary to improve our understanding of its pathology type 3 diabetes.

3. Glucagon-Like Peptide 1 (GLP1)

GLP-1 is an endogenous incretin hormone of 30-amino acids, produced by enteroendocrine L-cells, that influences food ingestion \[35,36\], enhances glucose-induced insulin secretion from pancreatic islets \[37\], and can act as a neuropeptide when released in the brain \[38\]. GLP-1 receptors (GLP-1R) exist widely throughout the brain, in areas including the hypothalamus, thalamus, hippocampus, cortex, and brainstem nucleus \[39–41\]. GLP-1 and other GLP-1 analogues can cross the BBB \[42,43\]. Because GLP-1 and its receptors exist in both the CNS and peripheral tissues, the effect of GLP-1 on energy metabolism is mediated by both the CNS and the peripheral nervous system (PNS) \[11,44,45\]. Moreover, GLP-1 is synthesized by neurons within the nucleus of the solitary tract \[46,47\]. These neurons have long projections to hypothalamic, thalamic, and cortical brain areas \[48\]. GLP-1 contributes to glycemic homeostasis and GLP1R agonists such as exendin-4, liraglutide, and lixisenatide have been approved to treat T2DM \[49,50\]. Furthermore, GLP-1 increases the spontaneous activity of neurons in the hippocampal CA1 region and promotes excitatory synaptic transmission in the hippocampus \[51\]. GLP-1 receptor knockout mice show decreased memory retention in the Morris water maze task, and the administration of GLP-1 agonists leads to improvement in learning and memory \[52\]. Here, given that GLP-1 could regulate glucose metabolism and potentially be used for treatment of T2DM \[44,49\], we focused on the role of GLP-1 in type 3 diabetes, highlighting the therapeutic importance of GLP-1 in diabetes-induced dementia.

4. The Effect of GLP-1 in Type 3 Diabetes: GLP-1 Attenuates Neuroinflammation and Improves Neurogenesis and Insulin Sensitivity in AD

One study suggested that GLP-1 mimetic drugs have neuroprotective, neurotrophic, and anti-inflammatory effects, which play a role in retardation of AD progression \[14\]. Another study demonstrated that liraglutide, a GLP-1 receptor agonist, can alleviate spatial memory dysfunction and neuroinflammation that leads to cognitive impairment \[53\]. GLP1 has been shown to act as a growth factor in the brain and promote neurite growth \[54\]. GLP-1 receptor activators stimulate the differentiation of neuronal stem cells in a manner similar to nerve growth factor, so it may inhibit brain atrophy in AD patients \[55\]. Additionally, GLP1 receptor agonists such as liraglutide and exendin-4 attenuate endogenous levels of amyloid beta in the brain and prevent amyloid plaque accumulation in the AD brain \[42,53\]. Furthermore, stimulating glucose metabolism in AD patients through the administration of GLP-1 markedly improves cognitive dysfunction in the AD brain \[56,57\]. In APP/PS1 mice (a mouse model of AD) brain, liraglutide and GLP-1 increase long-term potentiation (LTP) \[42,58\] and increase synaptic plasticity \[41,55,59\]. Moreover, GLP-1 has been found to improve insulin
sensitivity [60,61] and control energy metabolism [62,63]. Recent studies reported that GLP-1 could attenuate brain insulin resistance by decreasing c-Jun N-terminal kinase (JNK) signaling and increasing the expression of the B-cell lymphoma 2 gene (Bcl2) in the T2DM mouse [64]. One study demonstrated that liraglutide treatment in an AD mouse model triggers the activation of microglia in the brain [42]. Neurogenesis, the generation of new neurons from neuronal progenitor stem cells [65,66], occurs in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the hippocampal [67,68]. According to previous results, adult neurogenesis is linked to memory function and the facilitation of LTP [69,70]. In the AD brain, a decrease in neurogenesis is commonly observed and aggravates the disease pathology [41,71]. Several studies found that GLP-1 receptor agonists increase the proliferation of neural progenitor cells [41] and increase neurogenesis in the dentate gyrus of the hippocampus [43]. Earlier studies reported the impaired proliferation of neural stem cell in the AD mouse model [66,72] and that GLP-1 and analogues of GLP-1 can promote neural stem cell proliferation in the brain [73,74]. GLP-1 receptor activates neurogenesis in hippocampus through mitogen activated protein kinases (MAPK) [75], leading to enhancement of learning and memory [75–77]. Collectively, GLP-1 could attenuate neuroinflammation and enhance neurogenesis and insulin resistance in diabetes-induced dementia, also known as type 3 diabetes.

5. Conclusions

Summing up, we suggest that GLP-1 is a good candidate for improving cognitive dysfunction in diabetes-induced dementia. First, GLP-1 could attenuate the inflammatory responses in brain caused by amyloid beta (Aβ)-induced oxidative stress. GLP-1 could regulate the activation of microglia and protect neurons against oxidative stress. Second, GLP-1 could promote neurogenesis in AD brain. This means that GLP-1 could stimulate the generation of new neurons to replace damaged neurons in the AD brain. Finally, GLP-1 can alleviate insulin resistance in the AD brain, suggesting that impaired glucose metabolism and insulin resistance leads to severe memory dysfunction. To conclude, our study highlights that manipulation of GLP-1 may be an effective therapy for improving AD-like pathology in diabetes-induced dementia, also known as type 3 diabetes.

Acknowledgments: This study was supported by the Brain Research Program through the National Research Foundation of Korea funded by a grant from 2016R1D1A1B03930394.

Author Contributions: Juhyun Song contributed to writing the preliminary draft of this manuscript and revised the manuscript. Choon Sang Bae contributed to writing the draft and revising manuscript as a whole.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Querfurth, H.W.; LaFerla, F.M. Alzheimer’s disease. N. Engl. J. Med. 2010, 362, 329–344. [CrossRef] [PubMed]
2. LaFerla, F.M.; Green, K.N. Animal models of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2012, 2, a006320. [CrossRef] [PubMed]
3. Akter, K.; Lanza, E.A.; Martin, S.A.; Myronyuk, N.; Rua, M.; Raffa, R.B. Diabetes mellitus and Alzheimer’s disease: Shared pathology and treatment? Br. J. Clin. Pharmacol. 2011, 71, 365–376. [CrossRef] [PubMed]
4. Baglietto-Vargas, D.; Shi, J.; Yaeger, D.M.; Ager, R.; LaFerla, F.M. Diabetes and Alzheimer’s disease crosstalk. Neurosci. Biobehav. Rev. 2016, 64, 272–287. [CrossRef] [PubMed]
5. Mamelak, M. Energy and the Alzheimer brain. Neurosci. Biobehav. Rev. 2017, 75, 297–313. [CrossRef] [PubMed]
6. Roh, E.; Song, D.K.; Kim, M.S. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. Exp. Mol. Med. 2016, 48, e216. [CrossRef] [PubMed]
7. Roh, E.; Kim, M.S. Brain Regulation of Energy Metabolism. Endocrinol. Metab. 2016, 31, 519–524. [CrossRef] [PubMed]
8. Attwell, D.; Laughlin, S.B. An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow Metab. 2001, 21, 1133–1145. [CrossRef] [PubMed]
9. Magistretti, P.J.; Pellerin, L. Metabolic coupling during activation. A cellular view. Adv. Exp. Med. Biol. 1997, 413, 161–166. [PubMed]

10. Doraiswamy, P.M.; Sperling, R.A.; Coleman, R.E.; Johnson, K.A.; Reiman, E.M.; Davis, M.D.; Grundman, M.; Sabbagh, M.N.; Sadowsky, C.H.; Fleisher, A.S.; et al. Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: A multicenter study. Neurology 2012, 79, 1636–1644. [CrossRef] [PubMed]

11. Holst, J.J. The physiology of glucagon-like peptide 1. Physiol. Rev. 2007, 87, 1409–1439. [CrossRef] [PubMed]

12. Barrera, J.G.; Jones, K.R.; Herman, J.P.; D’Alessio, D.A.; Woods, S.C.; Seeley, R.J. Hyperphagia and increased fat accumulation in two models of chronic CNS glucagon-like peptide-1 loss of function. J. Neurosci. 2011, 31, 3904–3913. [CrossRef] [PubMed]

13. Sherwood, V. WNT signaling: An emerging mediator of cancer cell metabolism? Mol. Cell. Biol. 2015, 35, 20–10. [CrossRef] [PubMed]

14. Holscher, C. Central effects of GLP-1: New opportunities for treatments of neurodegenerative diseases. J. Endocrinol. 2014, 221, T31–T41. [CrossRef] [PubMed]

15. Talbot, K.; Wang, H.Y. The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer’s disease. Alzheimers Dement. 2014, 10, S12–S25. [CrossRef] [PubMed]

16. Peng, S.; Eidelberg, D.; Ma, Y. Brain network markers of abnormal cerebral glucose metabolism and blood flow in Parkinson’s disease. Neurosci. Bull. 2014, 30, 823–837. [CrossRef] [PubMed]

17. Berti, V.; Mosconi, L.; Pupi, A. Brain: Normal variations and benign findings in fluorodeoxyglucose-PET/computed tomography imaging. PET Clin. 2014, 9, 129–140. [CrossRef] [PubMed]

18. Carpenter, K.L.; Jalloh, I.; Gallagher, C.N.; Grice, P.; Howe, D.J.; Mason, A.; Timofeev, I.; Helmy, A.; Murphy, M.P.; Menon, D.K.; et al. 13C-labelled microdialysis studies of cerebral metabolism in TBI patients. Eur. J. Pharm. Sci. 2014, 57, 87–97. [CrossRef] [PubMed]

19. Tulppannen, A.M.; Lavikainen, P.; Solomon, A.; Kivipelto, M.; Uusitupa, M.; Soininen, H.; Hartikainen, S. History of medically treated diabetes and risk of Alzheimer disease in a nationwide case-control study. Diabetes Care 2013, 36, 2015–2019. [CrossRef] [PubMed]

20. Biessels, G.J.; Strachan, M.W.; Visseren, F.L.; Kappelle, L.J.; Whitmer, R.A. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: Towards targeted interventions. Lancet Diabetes Endocrinol. 2014, 2, 246–255. [CrossRef] [PubMed]

21. Butterfield, D.A.; Di Domenico, F.; Barone, E. Elevated risk of type 2 diabetes for development of Alzheimer disease: A key role for oxidative stress in brain. Biochim. Biophys. Acta 2014, 1842, 1693–1706. [CrossRef] [PubMed]

22. Bedse, G.; Di Domenico, F.; Serviddio, G.; Cassano, T. Aberrant insulin signaling in Alzheimer’s disease: Current knowledge. Front. Neurosci. 2015, 9, 204. [CrossRef] [PubMed]

23. Devaskar, S.U.; Giddings, S.J.; Rajakumar, P.A.; Carnaghi, L.R.; Menon, R.K.; Zahm, D.S. Insulin gene expression and insulin synthesis in mammalian neuronal cells. J. Biol. Chem. 1994, 269, 8445–8454. [PubMed]

24. Kuwabara, T.; Kagawa, M.; Onuma, Y.; Ito, Y.; Warashina, M.; Terashima, K.; Sanosaka, T.; Nakashima, K.; Gage, F.H.; Asashima, M. Insulin biosynthesis in neuronal progenitors derived from adult hippocampus and the olfactory bulb. EMBO Mol. Med. 2011, 3, 742–754. [CrossRef] [PubMed]

25. Banks, W.A.; Owen, J.B.; Erickson, M.A. Insulin in the brain: There and back again. Pharm. Ther. 2012, 136, 82–93. [CrossRef] [PubMed]

26. Le Roith, D.; Hendricks, S.A.; Lesniak, M.A.; Rishi, S.; Becker, K.L.; Havrankova, J.; Rosenzweig, J.L.; Brownstein, M.J.; Roth, J. Insulin in brain and other extrapancreatic tissues of vertebrates and nonvertebrates. Adv. Metab. Disord. 1983, 10, 303–340. [PubMed]

27. Kar, S.; Chabot, J.G.; Quirion, R. Quantitative autoradiographic localization of [125I] insulin-like growth factor I, [125I] insulin-like growth factor II, and [125I] insulin receptor binding sites in developing and adult rat brain. J. Comp. Neurol. 1993, 333, 375–397. [CrossRef] [PubMed]

28. O’Kusky, J.; Ye, P. Neurodevelopmental effects of insulin-like growth factor signaling. Front. Neuroendocrinol. 2012, 33, 230–251. [CrossRef] [PubMed]

29. Talbot, K.; Wang, H.Y.; Kazi, H.; Han, L.Y.; Bakshi, K.P.; Stucky, A.; Fuino, R.L.; Kawaguchi, K.R.; Samoyedny, A.J.; Wilson, R.S.; et al. Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J. Clin. Investig. 2012, 122, 1316–1338. [CrossRef] [PubMed]
30. Bloemer, J.; Bhattacharya, S.; Amin, R.; Suppiramaniam, V. Impaired insulin signaling and mechanisms of memory loss. *Prog. Mol. Biol. Transl. Sci.* 2014, 121, 413–449. [PubMed]

31. Faria, J.A.; Kinote, A.; Ignacio-Souza, L.M.; de Araujo, T.M.; Razolli, D.S.; Doneda, D.L.; Paschoal, L.B.; Lellis-Santos, C.; Bertolini, G.L.; Velloso, L.A.; et al. Melatonin acts through MT1/MT2 receptors to activate hypothalamic Akt and suppress hepatic gluconeogenesis in rats. *Am. J. Physiol. Endocrinol. Metab.* 2013, 305, E230–E242. [CrossRef] [PubMed]

32. O’Neill, C. PI3-kinase/Akt/mTOR signaling: Impaired on/off switches in aging, cognitive decline and Alzheimer’s disease. *Exp. Gerontol.* 2013, 48, 647–653. [CrossRef] [PubMed]

33. Kullmann, S.; Heni, M.; Veit, R.; Scheffler, K.; Machann, J.; Haring, H.U.; Fritsche, A.; Preissl, H. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* 2015, 38, 1040–1050. [CrossRef] [PubMed]

34. Zhu, X.; Perry, G.; Smith, M.A. Insulin signaling, diabetes mellitus and risk of Alzheimer disease. *J. Alzheimer’s Dis.* 2005, 7, 81–84. [CrossRef]

35. Stanley, S.; Wynne, K.; McGowan, B.; Bloom, S. Hormonal regulation of food intake. *Physiol. Rev.* 2005, 85, 1131–1158. [CrossRef] [PubMed]

36. Baggio, L.L.; Drucker, D.J. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007, 132, 2131–2157. [CrossRef] [PubMed]

37. Varndell, I.M.; Bishop, A.E.; Sikri, K.L.; Uttenthal, L.O.; Bloom, S.R.; Polak, J.M. Localization of glucagon-like peptide immunoreactants in human gut and pancreas using light and electron microscopic immunocytochemistry. *J. Histochem. Cytochem.* 1985, 33, 1080–1086. [CrossRef] [PubMed]

38. Holst, J.J.; Burcelin, R.; Nathansson, E. Neuroprotective properties of GLP-1: Theoretical and practical applications. *Curr. Med. Res. Opin.* 2011, 27, 547–558. [CrossRef] [PubMed]

39. Cork, S.C.; Richards, J.E.; Holt, M.K.; Gribble, F.M.; Reimann, F.; Trapp, S. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. *Mol. Metab.* 2015, 4, 718–731. [CrossRef] [PubMed]

40. Abbas, T.; Faivre, E.; Holscher, C. Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: Interaction between type 2 diabetes and Alzheimer’s disease. *Behav. Brain Res.* 2009, 205, 265–271. [CrossRef] [PubMed]

41. Hamilton, A.; Patterson, S.; Porter, D.; Gault, V.A.; Holscher, C. Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. *J. Neurosci. Res.* 2011, 89, 481–489. [CrossRef] [PubMed]

42. McClean, P.L.; Parthsarathy, V.; Faivre, E.; Holscher, C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer’s disease. *J. Neurosci.* 2011, 31, 6587–6594. [CrossRef] [PubMed]

43. Hunter, K.; Holscher, C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. *BMC Neurosci.* 2012, 13, 33. [CrossRef] [PubMed]

44. Hayes, M.R.; De Jonghe, B.C.; Kanozki, S.E. Role of the glucagon-like-peptide-1 receptor in the control of energy balance. *Physiol. Behav.* 2010, 100, 503–510. [CrossRef] [PubMed]

45. Williams, D.L.; Baskin, D.G.; Schwartz, M.W. Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. *Diabetes* 2006, 55, 3387–3393. [CrossRef] [PubMed]

46. Larsen, P.J.; Tang-Christensen, M.; Holst, J.J.; Orskov, C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience* 1997, 77, 257–270. [CrossRef]

47. Vrang, N.; Larsen, P.J. Preproglucagon derived peptides GLP-1, GLP-2 and oxyntomodulin in the CNS: Role of peripherally secreted and centrally produced peptides. *Prog. Neurobiol.* 2010, 92, 442–462. [CrossRef] [PubMed]

48. Llewellyn-Smith, I.J.; Reimann, F.; Gribble, F.M.; Trapp, S. Preproglucagon neurons project widely to autonomic control areas in the mouse brain. *Neuroscience* 2011, 180, 111–121. [CrossRef] [PubMed]

49. Lovshin, J.A.; Drucker, D.J. Incretin-based therapies for type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 2009, 5, 262–269. [CrossRef] [PubMed]

50. Vella, A.; Shah, P.; Reed, A.S.; Adkins, A.S.; Basu, R.; Rizza, R.A. Lack of effect of exendin-4 and glucagon-like peptide-1-(7,36)-amide on insulin action in non-diabetic humans. *Diabetologia* 2002, 45, 1410–1415. [PubMed]

51. Oka, J.I.; Goto, N.; Kameyama, T. Glucagon-like peptide-1 modulates neuronal activity in the rat’s hippocampus. *Neuroreport* 1999, 10, 1643–1646. [CrossRef] [PubMed]
62. Toft-Nielsen, M.B.; Damholt, M.B.; Madsbad, S.; Hilsted, L.M.; Hughes, T.E.; Michelsen, B.K.; Holst, J.J. The glucagon-like peptide 1 receptor agonist exendin-4 improves reference memory performance and decreases immobility in the forced swim test. *Eur. J. Pharm.* 2011, 650, 249–255. [CrossRef] [PubMed]

53. McLean, P.L.; Holscher, C. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer’s disease. *Neuropharmacology* 2014, 76, 57–67. [CrossRef] [PubMed]

54. Hayes, M.R. Neuronal and intracellular signaling pathways mediating GLP-1 energy balance and glycemic effects. *Physiol. Behav.* 2012, 106, 413–416. [CrossRef] [PubMed]

55. Salcedo, I.; Tweedie, D.; Li, Y.; Greig, N.H. Neuroprotective and neurotrophic actions of glucagon-like peptide-1: An emerging opportunity to treat neurodegenerative and cerebrovascular disorders. *Br. J. Pharm.* 2012, 166, 1586–1599. [CrossRef] [PubMed]

56. Parthsarathy, 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, e58784. [CrossRef] [PubMed]

57. Craft, S.; Baker, L.D.; Montine, T.J.; Minoshima, S.; Watson, G.S.; Claxton, A.; Arbuckle, M.; Callaghan, M.; Tsai, E.; Plymate, S.R.; et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: A pilot clinical trial. *Arch. Neurol.* 2012, 69, 29–38. [CrossRef] [PubMed]

58. McLean, P.L.; Gault, V.A.; Harriott, P.; Holscher, C. Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: A link between diabetes and Alzheimer’s disease. *Eur. J. Pharm.* 2010, 630, 158–162. [CrossRef] [PubMed]

59. Darsalia, V.; Hua, S.; Larsson, M.; Mallard, C.; Nathanson, D.; Nystrom, T.; Sjoholm, A.; Johansson, M.E.; Patrone, C. Exendin-4 reduces ischemic brain injury in normal and aged type 2 diabetic mice and promotes microglial M2 polarization. *PLoS ONE* 2014, 9, e103114. [CrossRef] [PubMed]

60. Adamska, E.; Ostrowska, L.; Gorska, M.; Kretowski, A. The role of gastrointestinal hormones in the pathogenesis of obesity and type 2 diabetes. *Przegląd Gastroenterol.* 2014, 9, 69–76. [CrossRef] [PubMed]

61. Ravassa, S.; Beaumont, J.; Huerta, A.; Barba, J.; Coma-Canella, I.; Gonzalez, A.; Lopez, B.; Diez, J. Association of low GLP-1 with oxidative stress is related to cardiac disease and outcome in patients with type 2 diabetes mellitus: A pilot study. *Free Radic. Biol. Med.* 2015, 81, 1–12. [CrossRef] [PubMed]

62. Toft-Nielsen, M.B.; Damholt, M.B.; Madsbad, S.; Hilsted, L.M.; Hughes, T.E.; Michelsen, B.K.; Holst, J.J. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J. Clin. Endocrinol. Metab.* 2001, 86, 3717–3723. [CrossRef] [PubMed]

63. Vilsboll, T.; Krarup, T.; Deacon, C.F.; Madsbad, S.; Holst, J.J. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes* 2001, 50, 609–613. [CrossRef] [PubMed]

64. Candeias, E.; Sebastiao, I.; Cardoso, S.; Carvalho, C.; Santos, M.S.; Oliveira, C.R.; Moreira, P.I.; Duarte, A.I. Brain GLP-1/IGF-1 Signaling and Autophagy Mediate Exendin-4 Protection Against Apoptosis in Type 2 Diabetic Rats. *Mol. Neurobiol.* 2017. [CrossRef] [PubMed]

65. Emsley, J.G.; Mitchell, B.D.; Kempermann, G.; Macklis, J.D. Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. *Prog. Neurobiol.* 2005, 75, 321–341. [CrossRef] [PubMed]

66. Hamilton, A.; Holscher, C. The effect of ageing on neurogenesis and oxidative stress in the APP(swe)/PS1(deltaE9) mouse model of Alzheimer’s disease. *Brain Res.* 2012, 1449, 83–93. [CrossRef] [PubMed]

67. Cameron, H.A.; McKay, R.D. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. *J. Comp. Neurol.* 2001, 435, 406–417. [CrossRef] [PubMed]

68. Abrous, D.N.; Koehl, M.; Le Moal, M. Adult neurogenesis: From precursors to network and physiology. *Physiol. Rev.* 2005, 85, 523–569. [CrossRef] [PubMed]

69. Bruel-Jungerman, E.; Davis, S.; Rampon, C.; Laroche, S. Long-term potentiation enhances neurogenesis in the adult dentate gyrus. *J. Neurosci.* 2006, 26, 5888–5893. [CrossRef] [PubMed]

70. Van Praag, H.; Shubert, T.; Zhao, C.; Gage, F.H. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* 2005, 25, 8680–8685. [CrossRef] [PubMed]

71. Harkavyi, A.; Abuirmeileh, A.; Lever, R.; Kingsbury, A.E.; Biggs, C.S.; Whitton, P.S. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson’s disease. *J. Neuroinflamm.* 2008, 5, 19. [CrossRef] [PubMed]
72. Faure, A.; Verret, L.; Bozon, B.; El Tayara, N.E.T.; Ly, M.; Kober, F.; Dhenain, M.; Rampon, C.; Delatour, B. Impaired neurogenesis, neuronal loss, and brain functional deficits in the APPxPS1-Ki mouse model of Alzheimer’s disease. *Neurobiol. Aging* **2011**, *32*, 407–418. [CrossRef] [PubMed]

73. Bertilsson, G.; Patrone, C.; Zachrisson, O.; Andersson, A.; Dannaeus, K.; Heidrich, J.; Kortesmaa, J.; Mercer, A.; Nielsen, E.; Ronnholm, H.; et al. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson’s disease. *J. Neurosci. Res.* **2008**, *86*, 326–338. [CrossRef] [PubMed]

74. Drucker, D.J. Glucagon-like peptides: Regulators of cell proliferation, differentiation, and apoptosis. *Mol. Endocrinol.* **2003**, *17*, 161–171. [CrossRef] [PubMed]

75. During, M.J.; Cao, L.; Zuzga, D.S.; Francis, J.S.; Fitzsimons, H.L.; Jiao, X.; Bland, R.J.; Klugmann, M.; Banks, W.A.; Drucker, D.J.; et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat. Med.* **2003**, *9*, 1173–1179. [CrossRef] [PubMed]

76. Raber, J.; Rola, R.; LeFevour, A.; Morhardt, D.; Curley, J.; Mizumatsu, S.; VandenBerg, S.R.; Fike, J.R. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat. Res.* **2004**, *162*, 39–47. [CrossRef] [PubMed]

77. Snyder, J.S.; Hong, N.S.; McDonald, R.J.; Wojtowicz, J.M. A role for adult neurogenesis in spatial long-term memory. *Neuroscience* **2005**, *130*, 843–852. [CrossRef] [PubMed]