Neuroprotective role of GLP-1 receptor agonists

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Neuroprotective role of GLP-1 receptor agonists

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Alzheimer's disease & other dementias

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Research Abstract

Type 2 diabetes mellitus (T2DM) is a prevalent disease in the elderly for which current treatments are available, but not satisfactory. It is a chronic, age-related degenerative disorder

that is a leading cause of morbidity and mortality in the elderly, and has attained epidemic proportion, with in excess of 171 afflicted worldwide (Wild et al., Diabetes Care 27:104753, 2004). A variety of risk factors have been implicated in the development of T2DM (Gtz et al., Cell Mol Life Sci 66:1321-5, 2009; Jin & Patti, Clin Sci (Lond) 116:99-111, 2009), including a genetic predisposition, age, oxidative stress, obesity, diet, and physical inactivity. By comparison, several of these same factors appear to be involved in neurodegenerative disorders, such as Alzheimer's disease (AD), the most common form of dementia (Reddy et al., J Alzheimers Dis 16:763-74, 2009; Luchsinger & Gustafson, J Alzheimers Dis 16:693-704, 2009). Interestingly, a number of well-designed epidemiological studies have established a link between these two diseases, together with others, including Parkinson's disease (PD) and stroke, identifying T2DM as a risk factor for developing various chronic and acute neurodegenerative disorders (Toro et al., J Alzheimers Dis 16:687-91, 2009; Craft, Curr Alzheimer Res 4:147-52, 2007). The pancreas and brain are both highly insulin sensitive tissues. T2DM and AD, together with other neurological conditions, share several clinical and biochemical features. Particularly important amongst these is an impaired insulin signaling, suggesting overlapping pathogenic mechanisms. Hence, an effective treatment strategy in one disease could have potential value in the other. A recent effective treatment strategy in T2DM is the use of incretin-based therapies based on the insulinotropic actions of the endogenous peptide, glucagon-like peptide-1 (GLP-1), utilizing the long-acting analog exendin-4 (Ex-4) (Lovshin & Drucker, Nat Rev Endocrinol 5:262-9, 2009; Drucker, Diabetes 62:3316-23, 2013). The acute actions of GLP-1 and receptor (R) agonists on beta-cells include stimulation of glucose-dependent insulin release, augmentation of insulin biosynthesis and stimulation of insulin gene transcription. Chronic actions include stimulation of beta-cell proliferation, induction of islet neogenesis and inhibition of beta-cell apoptosis that, together, promote expansion of beta-cell mass and the normalization of insulin signaling (Drucker, Diabetes 64:317-26, 2015). Ex-4 has been reported to readily enter the brain (Kastin et al., Int J Obes Relat Metab Disord 27:313-8, 2003), where the GLP-1R is expressed widely (Perry & Greig, Trends Pharmacol Sci 24:377-83, 2003) and its activation results in multiple biological responses. GLP-1R stimulation in brain is classically allied to regulation of appetite and satiety (Lovshin & Drucker ibid, 2008). More recently, however, it has been associated with neurotrophic (Perry et al., J Pharmacol Exp Ther 300:958-66, 2002) and neuroprotective actions in both cellular and in vivo models of acute and chronic neurodegenerative conditions (Perry et al., J Pharmacol Exp There 302:881-8., 2002; Perry et al., J Neurosci Res 72:603-12, 2003), including stroke, AD, PD and Huntingtons disease (HD) (Li et al., PNAS 106:1285-90, 2009; Li et al., J Alz Dis 19:1205-19, 2010; Harkavyi et al., J Neuroinflamm 21:519, 2008; Martin et al., Diabetes 58:318-28, 2009; Bertilsson et al., J Neurosci Res 86:326-38, 2008). Our target for drug design is the glucagon-like peptide-1 (GLP-1) receptor (R). GLP-1 is secreted from the gut in response to food and is a potent secretagogue that binds to the GLP-1R on pancreatic beta-cells to induce glucose-dependent insulin secretion, thereby controling plasma glucose levels. We are developing long-acting GLP-1 analogues (collaborators: Drs. Egan, Mattson). This research aided in the development of the peptide exendin-4 (Ex-4) into clinicall studies in type 2 diabetes. Novel chimeric peptides that combine the best features of GLP-1 and Ex-4 have also been designed and assessed in a variety preclinical models (Wang et al., J Clin Invest 99:2883-9, 1997, DeOre et al., J Gerontol A Biol Sci Med Sci 52:B245-9, 1997; Greig et al., Diabetologia 42:45-50, 1999; Szayna et al., Endocrinol 141:1936-41, 2000; Doyle et al., Endocrinol 142:4462-8, 2001; Doyle et al., Regul Pept 114:153-8, 2003; Doyle et al., Endocrine 27:1-9, 2005). We are characterizing the role of GLP-1R stimulation in the nervous system, as it is found present in brain and peripheral nerve.

Our collaborative studies were the first to define that GLP-1 analogues possess neurotrophic properties and protect neuronal cells from a wide variety of lethal insults. Neuroprotection in cell culture translated to in vivo studies in classical rodent neurodegeneration models, which include AD, stroke, PD, HD, ALS, traumatic brain injury and peripheral neuropathy (Perry et al., Exp Neurol 203:293-301, 2007; Li et al., PNAS 106:1285-90, 2009; Li et al., J Alz Dis. 19:1205-19, 2010, Li et al., PLoS One 7:e32008, 2012; Salcedo et al., Br J Pharmacol 166:1586-99, 2012; Tweedie et al., Exp Neurol 239:170-82, 2013; Rachmany et al., Age 35:1621-36, 2013; Tweedie et al., Neurobiol Dis 54:1-11, 2013; Eakin et al., PLoS One 8:e82016, 2013; Greig et al., Alzheimers Dement. 10(S1):S62-7, 2014; Tweedie et al., Alzheimers Dement. 12:34-48, 2016). Current studies are focused on selecting agents for clinical assessment and defining mechanisms underpinning the neurotrophic/neuroprotective actions (Li et al., J Neurochem 113:621-31, 2010; Li et al., J Neurochem 135:1203-17, 2015). Additional research is focused on optimizing the translation of Ex-4 for the treatment of neurodegenerative disorders, and defining which specific disorders are most likely to have a clinical response – in this regard, the long-acting GLP-1 receptor agonist exendin-4 is in a current clinical trial in MCI/early AD (Collaborators: Drs. Kapogiannis, Egan, Mattson) and other clinical trials in different disorders are in current planning involving a sustained-release formulation of Ex-4 (PT302, Peptron, S. Korea) (Collaborators: Drs. Kim and Peptron colleagues; Hoffer; Chiang, Wang, Pick). An alternate approach is to augment the levels of endogenous incretins available within the body by inhibiting their metabolism and, thereby, elevate their levels. In this regard, GLP-1 and the incretin, glucose-dependent insulinotropic polypeptide (GIP) are released following food ingestion and bind to their respective receptors on pancreatic beta cells to induce insulin secretion. Receptors for these endogenous peptides are found throughout the body, including the brain – which both GLP-1 and GIP can readily enter. The presence of the metabolizing serine protease enzyme, dipeptidyl peptidase-4 (DPP-4), results in the rapid clearance of both incretins. Current studies are assessing the utility of selective and well tolerated DPP-4 inhibitors in cellular and preclinical animal studies to elevate available GLP-1 and GIP levels in plasma and brain to a level at which they may provide neurotrophic/protective actions for the treatment of neurodegenerative disorders. Still other approaches being evaluated involve augmenting GIP-R and GLP-1R stimulation separately and together via other techniques. Ongoing studies are in preclinical stages to both evaluate new drug development and drug repurposing towards neurological disorders currently lacking effective pharmacological treatment where this incretin strategy could prove highly beneficial (Collaborators: Drs. Wang, Hoffer, Tones, Zaleska, Mattison, Kim, DiMarchi).

Lay Summary
Further information available at:

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Investments > €500k

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