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GLP-1 Mediated Mechanisms in the Diabetic Mouse Retina

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The incidence of T1DM and T2DM will continue to increase for the foreseeable future. DR incidence is expected to increase for the foreseeable future as well. DR can be subdivided into NPDR and PDR. Tight blood glucose control and blood pressure optimization remain the most effective primary and secondary treatment of DR. While treat-ments exist for moderately severe to severe NPDR and all PDR forms, these treat ments remain tertiary in nature as they only prevent DR complications and DR progression. Currently, a dearth of DR preventions and treatments for mild/moderate NPDR leaves many DM patients with no proper primary and secondary DR treatment options besides tight blood glucose control and blood pressure optimization.

The dearth of early DR treatments reflects a lack of understanding of DR mechanisms. While its results still have not yielded such a therapy, the DCCT/EDIC longitudinal clin-ical trials illustrate how hyperglycemic memory offers an alternative mechanistic explanation to chronic hyperglycemia in the manifestation of DR. Michael Brownlee proposed that HGM occurs when transient hyperglycemia increases ROS production, up-regulates PARP, and activates four independent HGM molecular mechanisms. This ROS production depends on a mitochondrial ROS loop.

A metabolic product of GLP-1 – GLP-1 9,36 amide – has been shown to interrupt the ROS loop in human aortic endothelial cells. GLP-1a and DPP-IVi should theoretically decrease GLP-1 9, 36 amide concentration, exacerbate the ROS loop, and lead to increased HGM driven DR.

Yet, some pre-clinical studies indicate otherwise. These studies report GLP-1/DPP-Ivi mediated mitigation of HGM driven DR in HUVEC cells, C. elegans, and STZ-Wistar rats. STZ-C57Bl6J mice have also been shown to demonstrate HGM driven DR through persistent transcriptomic changes to the cytoskeletal/nuclear compartments and persistent pericyte dropout despite reinstatement of euglycemia via islet cell transplantation.

Pericytes are a component of the retinal NVU thought to be where DR manifests. NVU components affected by DR include but are not limited to glial NVU cells such as microglia and Müller glia; neuroretinal NVU cells such as photoreceptors and bipolar cells; and vascular NVU cells and vessels such as pericytes, endothelial cells, and acellular capillaries.

This study investigates STZ-C57Bl6J mice to induce hyperglycemia in mice, reveal HGM-dependent and HGM-independent effects of the GLP1-a lixisenatide and the DPP-IVi linagliptin on DR, and analyze the transcriptomic effects of lixisenatide and linagliptin on diabetes-induced genes in DR.

As expected, diabetic controls and treatment groups demonstrated hyperglycemia, high %HbA1c values, and weight loss relative to non-diabetic controls. Controls exhibted no histomorphological manifestations of HGM, no increases in methylglyoxal concentration, and no neuroretinal dysfunction at both 6 and 12 weeks after diabetes induction. This places the mice clinically in a pre-DR stage.

Control groups demonstrated transcriptomic changes in genes involved in cell adhesion (Pcdhgb8, itga10), fatty acid transport (Slc27a3), and reseting the vision cycle (Gucy2e) while not showing transcriptomic changes conducive to initial neuroprotection and cell survival but future neovascularization (VEGF-A) or inflammation. All groups did not demonstrate the transcriptomic changes reported in the cytoskeletal and nuclear compartments of this model in earlier studies.

While the control groups showed a modest amount of differentially expressed genes, both lixisenatide and linagliptin significantly expressed 10x as many genes relative to non-diabetic controls while hardly differentially expressing genes relative to diabetic controls. They also did not alleviate the transcriptomic changes involved in cell adhesion, fatty acid transport, or resetting the vision cycle.

Furthermore, both lixisenatide and linagliptin demonstrated neuroretinal dysfunction relative to all controls through a decrease in the mfERG b-wave amplitude. Both SUSTAIN-6 and LEADER implicate the GLP-1a semaglutide and liraglutide respectively in increased DR complications. This study controlled for the SUSTAIN-6 cofounders of prior DR (The mice are pre-DR), prior insulin treatment (The

mice received no prior insulin treatment), and rapid %HbA1c reduction (The mice report no %HbA1c reductions). GLP-1a have recently been approved for weight loss and will thus have an ever-increasing role in the clinic. The neuroretinal dysfunction in this report as well as the SUSTAIN-6 and LEADER results merit a longitudinal study of long-term GLP-1a or DPP-IV treatment effects on not only DR complications as measured by fundoscopy but also neuroretinal dysfunction as measured by mfERG.

This study reports that the time to diabetic retinopathy is variable in mice. Thus, this study cannot make definitive conclusions about genes associated with HGM. This study reports that, in the absence of endogenous insulin production, lixisenatide and linagliptin move the retinal transcriptome away from healthy retinal gene expression while hardly altering the diabetic retinal transcriptome in pre-DR. Lixisenatide and linagliptin do not rescue genes potentially associated with diabetic retinopathy such as cell adhesion genes (Pcdghb8, itga10), a fatty acid transport gene (Slc27a3), and a gene responsible for resetting the vision cycle (Gucy2e). This study also reports retinal dysfunction correlated with lixisenatide and linagliptin.

While these results will not lesson the increased DR burden expected by 2045, they do contextualize the role of GLP-1a and DPP-IVi in pre-DR while identifying potential gene targets that may or may not be driven by HGM. (pages 44 – 45)