Fundació La Marató de TV3
22nd SYMPOSIUM
Diabetes and Obesity

TOPICAL ADMINISTRATION OF GLP-1: A NEW STRATEGY FOR TREATMENT OF DIABETIC RETINOPATHY

Rafael Simó Canonge

VHIR Institut de Recerca Hospital Universitari Vall d'Hebron

1. Summary

Background and hypothesis

Diabetic retinopathy (DR) remains the leading cause of blindness among working-age individuals in developed countries. Current treatments target late stages of DR and preventional/interventional strategies against early stages of DR are urgently needed. In this regard, there is growing evidence that retinal neurodegeneration plays an essential role in the development of DR and the use of eye drops containing neuroprotective agents has been envisaged as an emergent area of interest.

We have recently demonstrated that topical administration of GLP-1R agonists prevents retinal neurodegeneration and the breakdown of the blood-retinal barrier. Therefore, it seems reasonable to hypothesize that GLP-1R agonists will have a significant role in the treatment of early stages of DR.

Main objectives

The main objectives of the proposal are the following:

1. To further explore the mechanisms involved in neuroprotection conferred by topical administration of GLP-1.
2. To examine the link between neuron and microvascular protection mediated by GLP-1.
3. To perform studies of dose-effectiveness and pharmacokinetics of native GLP-1 administered by topical route (eye drops).

Additional aims:

1) To explore whether there is a progressive decrease of GLP-1 production in human retinas in relation to age and diabetes duration.
2) To examine whether topical administration of DPP-4 inhibitors are effective in preventing diabetes-induced retinal neurodegeneration (proof of principal).

Expected results

Our results will permit us to gain new insights into the molecular mechanisms involved in the beneficial effects of GLP-1 the early stages of DR and would pave the way for future clinical trials. Overall, our proposal will impact on general community and health care systems in terms of improving diabetes care and reducing the economic burden related to this devastating complication of diabetes.

2. Results

The main results obtained in relation to the objectives set are summarized:

Mechanisms involved in the beneficial action of GLP-1 in the retina: neuroprotection and prevention of microvascular abnormalities

The mechanisms by which GLP-1 prevents retinal neurodegeneration and prevents initial microvascular alterations (disruption of the blood-retinal barrier) induced by diabetes in an experimental model (db/db mouse) have been investigated. We have found that neuroprotective action occurs by induction of survival signaling (i.e. AKT phosphorylation) and by its effect on glutamate metabolism. In addition, we have observed that GLP-1 has a potent anti-inflammatory effect.

GLP-1 expression in human retinas

GLP-1 expression has been shown to be present in human retinas and is decreased in the retinas of diabetic donors. However, we did not detect differences in GLP-1 receptor expression in retinas of diabetic donors with no, or only mild, retinopathy compared with retinas of non-diabetic donors.

Effect of DPP-4 inhibition on GLP-1 content in retina and its role in diabetes-induced neurovascular disorders

We observed that two DPP-4 inhibitors (saxagliptin and sitagliptin), administered topically by the eye, produce a significant increase in GLP-1 content in the retina and prevent neurodegeneration and vascular extravasation due to blood-retinal barrier disruption in diabetic mice (db/db model).

Pharmacokinetics and dose-efficacy studies of GLP-1

The ocular distribution of topically administered GLP-1 was evaluated in rabbits. The dose-effectiveness study was performed in db/db mice to assess the minimum effective dose of GLP-1 to have the maximum effect on neurovascular retinal disorders induced by diabetes.

3. Impact

The results obtained constituted a relevant part of the pre-clinical dossier that was presented to the AEMPs (Spanish Agency for Medicines and Health Products) to request the initiation of clinical trials with GLP-1 in eye drops. The AEMPS approved the start of Phase I *(Phase I clinical trial, single and multiple ascending dose, randomized (2: 1), double-blind, placebo-controlled, in parallel, to evaluate the safety and tolerability of topical administration ocular, of two doses of FAB120 in participants with type 2 diabetes. EUDRACT number: 2019-002502-52).* This clinical trial was designed by the project's PI and team and was conducted in collaboration with the Ophthalmology Department at Vall d'Hebron University Hospital (August-December 2020). The topically administered drug has been shown to be safe and the Phase II clinical trial to evaluate efficacy and safety is currently being prepared.

It must be noted that DR remains the most common cause of vision impairment in working adults in the US and Europe, and its prevalence remains around 30% in cross-sectional studies worldwide. Healthcare costs for diabetic patients are more than double the costs of those without diabetes, and the average healthcare costs increases considerably with the severity of DR. Preventing the progression of DR treating the early stages of the disease using topical administration of GLP-1 will not only improve the quality of life of the diabetic population but will also significantly reduce the healthcare costs.

4. Publications

Hernández C, Bogdanov P, Solà-Adell C, Sampedro J, Valeri M, Genís X, Simó-Servat O, García-Ramírez M, Simó R. Topical administration of DPP-IV inhibitors prevents retinal neurodegeneration in experimental diabetes. Diabetologia. 2017;60(11):2285-2298

Yeste J, García-Ramírez M, Illa X, Guimerà A, Hernández C, Simó R, Villa R. A compartmentalized microfluidic chip with crisscross microgrooves and

electrophysiological electrodes for modeling the blood-retinal barrier. Lab Chip. 2017;18(1):95-105

Sampedro J, Bogdanov P, Ramos H, Solà-Adell C, Turch M, Valeri M, Simó-Servat O, Lagunas C, Simó R, Hernández C. New Insights into the Mechanisms of Action of Topical Administration of GLP-1 in an Experimental Model of Diabetic Retinopathy. J Clin Med. 2019 Mar 11;8(3):339.

Ramos H, Bogdanov P, Sampedro J, Huerta J, Simó R, Hernández C. Beneficial Effects of Glucagon-Like Peptide-1 (GLP-1) in Diabetes-Induced Retinal Abnormalities: Involvement of Oxidative Stress. Antioxidants (Basel). 2020 Sep 10;9(9):E846

Simó R, Bogdanov P, Ramos H, Huerta J, Simó-Servat O, Hernández C. Effects of topical administration of semaglutide on retinal neuroinflammation and vascular leakage in experimental diabetes. Diabetologia (Under review)