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Topical ocular administration of DPP-IV inhibitors: a new approach for treating diabetes-induced retinal neurodegeneration

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Retinal neurodegeneration plays a significant role in the pathogenesis of diabetic retinopathy (DR), the leading cause of preventable blindness. In fact, the American Diabetes Association has defined DR as a highly specific neurovascular complication (Solomon et al., 2017). Therefore, it is no longer acceptable to consider DR as merely a microvascular complication. In this regard, the term diabetic retinal disease (DRD) has been proposed as a broader term comprising microangiopathy and neurodegeneration. However, there are currently no treatments available that directly target the neurodegenerative changes of DR. This paper will give new insights into the translational research in this field with particular emphasis on glucagon-like peptide 1/dipeptidyl peptidase IV (GLP-1/DPP-IV) inhibitors.

Replacement of neuroprotective factors synthesized by the retina: The current approved treatment for DRD is targeting advanced stages of the disease and is based on laser photocoagulation and/or intravitreal injections of corticosteroids or anti-vascular endothelial growth factor agents. These treatments are aggressive, expensive and with significant adverse effects, therefore, new strategies aimed at treating the early stages of DRD are urgently needed.

Neurovascular unit impairment is an early event in the pathogenesis of DR, which comprises a complex interplay of microvascular abnormalities and neurodegeneration. Experimental evidence shows that by treating neurodegeneration microvascular disease (i.e. vascular leakage) can be prevented, thus confirming the significant cross-talk that exists between neurons/glial cells and microvasculature (endothelium and pericytes) (Simó et al., 2021).

The molecular mediators of diabetes-induced retinal neurodegeneration include pro-inflammatory cytokines, oxidative stress, mitochondrial dysfunction, extracellular glutamate accumulation, and the molecular pathways closely related to chronic hyperglycemia. Notably, the diabetic milieu causes the downregulation of several proteins synthesized by the retina with neurotrophic activity such as interphotoreceptor retinoid-blinding protein, pigment epithelium-derived factor, somatostatin (SST), and GLP-1. Therefore, the replacement of these neuroprotective factors together with optimization of metabolic control is a reasonable approach for preventing retinal neurodegeneration (Simó et al., 2021).

The neuroprotective effects of SST administered by eye drops in streptozotocin-induced diabetic rats were the experimental proof of concept to build up the EUROCONDOR study, a phase II–III randomized clinical trial showing that SST administered by eye drops was able to arrest the progression of retinal neurodysfunction in type 2 diabetic patients (Simó et al., 2019). However, no effect in preventing or arresting microvascular disease was observed. In addition, neurodegeneration does not appear in a significant proportion (30%) of patients in whom early stages of the microvascular disease have already exited. This data points to screening retinal neurodysfunction as an essential procedure for selecting those patients in whom neuroprotective treatment might be useful. Another lesson of the EUROCONDOR study was that topical ocular administration of small peptides can reach the retina by the transscleral route. This finding opened up a new approach to treating DR, and in terms of clinical practice is significant because it can avoid the use of intravitreal injections, which otherwise can hardly be proposed at these early stages of DR.

Topical administration (eye drops) of GLP-1 and GLP-1 receptor agonists was also able to prevent the two hallmarks of neurodegeneration (apoptosis and glial activation) in db/db mouse (an experimental model of type 2 diabetes). Consequently, a significant effect in reducing the neuroretinal thinning and functional abnormalities detected by electroretinography was observed (Hernández et al., 2016). In addition, GLP-1 administered by eye drops restored the number of cells in the retinal layers (ganglion, inner and outer neuron cell layers) to the same level as that observed in non-diabetic mice, and this effect was associated with a significant increase in retinal Ki67, a marker of cellular proliferation (Sampedro et al., 2019). This finding was not reported with SST and it means that GLP-1 is not only a neuroprotective agent but also could participate in retinal neurogenesis. In addition, these neuroprotective/neuroregenerative properties were associated with a significant effect in preventing diabetes-induced vascular leakage, another effect that was not observed with SST. This dual neurotropic and vasculotropic effect place GLP-1 as an excellent candidate for treating the early stages of DR by targeting the neurovascular unit as a whole. It is worth mentioning that topical ocular administration of GLP-1 was unable to reduce blood glucose levels and, therefore, all the effects above mentioned should be attributed to the GLP-1 itself. In addition, the lack of effect in blood glucose levels precludes a potential early worsening of DRD due to the rapid decrease in HbA1c.

DPP-IV inhibitors a new approach for treating DR: GLP-1 is extremely susceptible to being rapidly degraded by the enzyme DPP-IV, which also exists in the human retina and is more abundant in patients with diabetes (Hernández et al., 2017). Since GLP-1 is produced by the retina and is downregulated by the diabetic milieu, it is reasonable to hypothesize that the inhibition of DPP-IV could enhance GLP-1, thus preserving its autocrine/paracrine neuroprotective effects. In addition, this strategy could also prevent the degradation of serum-derived GLP-1 that reaches the retina through the blood-retinal barrier. This hypothesis has recently been confirmed in db/db mice treated with eye drops of sitagliptin and saxagliptin (two DPP-IV inhibitors) (Hernández et al., 2017). The results, in terms of preventing neurodegeneration, were similar to or even better than those obtained by using GLP-1 or GLP-1 receptor agonists. In addition, both DPP-IV inhibitors were able to significantly increase the levels of exchange protein activated by cAMP-1. This protein is a downstream cAMP signaling mediator and could play an important role in the maintenance of the endothelial barrier and neuronal functions in the retina. As occurs with GLP-1, blood glucose levels are not reduced by DPP-IV inhibitors administered by eye drops, thus indicating its direct neurovascular protective effect.

Mechanisms involved in the beneficial action of DPP-IV inhibitors on the diabetic retina: Although GLP-1 enhancement seems one of the main mechanisms involved in the beneficial action of DPP-IV inhibitors, other unrelated mechanisms cannot be ruled out. It should be noted that linagliptin (a DPP-IV inhibitor) exerts a neuroprotective effect in *C. elegans*, a model lacking GLP-1, thus indicating the neuroprotective GLP-1 independent effects of linagliptin and probably of all the family of DPP-IV inhibitors (Dietrich et al., 2016). The main mechanisms involved in the beneficial actions of DPP-IV inhibitors on the neurovascular unit are represented in **Figure 1**.

DPP-IV inhibitors reduce brain damage and improve neural damage and functional parameters after stroke in various animal models via several mechanisms including reduction of inflammation, oxidative stress, excitotoxicity, and endothelial leakage independently of their control of glucose homeostasis (Darsalia et al., 2019). These mechanisms seem also involved in the protection of neuroretinal damage induced by diabetes. Recently, we found that sitagliptin administered by eye drops prevented the downregulation of presynaptic proteins involved in vesicle biogenesis, mobilization and docking, membrane fusion and recycling, and synaptic neurotransmission in db/db mice (Ramos et al., 2021). It is unclear whether GLP-1 enhancement plays a role if any in all these neuroprotective mechanisms.

There are two mechanisms related to neuroprotection and regeneration reported with DPPIV-inhibitors that deserve specific research in DRD and that are unrelated to GLP-1. One is related to senescence and the other to neuroregeneration.

Cellular senescence is classically characterized as irreversible cell cycle arrest. Cells alter gene expression, resulting in the production of

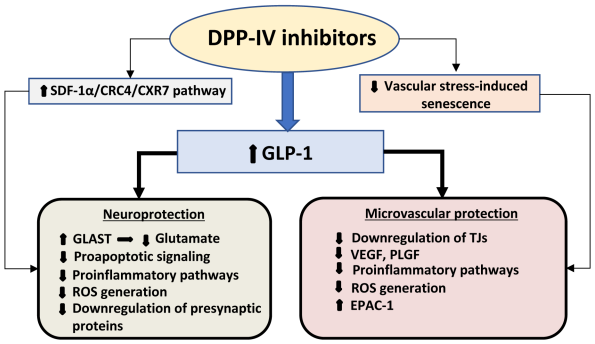

Figure 1 | **Mechanisms involved in the beneficial actions of DPP-IV inhibitors on the neurovascular unit of the diabetic retina.**
Two types of actions can be observed: related and unrelated to the enhancement of GLP-1. It is still unknown whether some of the actions represented as mediated by the increase of GLP-1 can also be exerted by DPP-IV inhibitors *per se*. Created using Microsoft PowerPoint. DPP-IV: Dipeptidyl peptidase IV; EPAC: exchange protein directly activated by cAMP; GLP-1: glucagon-like peptide 1; PLGF: placental growth factor; ROS: reactive oxygen species; TJs: tight junctions; VEGF: vascular endothelial growth factor.

proinflammatory, and matrix-degrading molecules known as the senescent-associated secretory phenotype. The inhibition of DPP-IV by anagliptin protects human vascular endothelial cells against stress-induced accelerated senescence (Kang et al., 2021).

In addition, the inhibition of DPP-IV activity reduces the degradation of SDF-1α and potentiates the SDF-1α/CXCR4/CXCR7 signaling pathway, which plays an important role in the process of neurogenesis by influencing the migration, proliferation, and differentiation of the neuroprogenitor cells (Cheng et al., 2017). This effect is unrelated to the increase of GLP-1 and suggests a potential regenerative effect of DPP-IV inhibitors that should be investigated in appropriate animal models. In this regard zebrafish, due to their small size, low cost, and ability to regenerate after some injuries, is a convenient animal model for retinal neuroprotection and regeneration research. Additionally, their vision is cone-dominated, like humans, and their eye structure and development are well-conserved across vertebrate species. Consequently, more researchers have turned to zebrafish to study retinal neurodegenerative diseases.

Concluding remarks and new perspectives: Neuroprotection based on the molecules that are downregulated in the diabetic retina is a rational approach for treating DRD, and it is expected that will be the subject of clinical trials very soon. The accumulated experimental evidence suggests that the replacement of GLP-1 seems a very good option, but DPP-IV inhibitors are cheaper and more stable than GLP-1. This is a significant advantage when planning a clinical development. In addition, the pleiotropic actions of DPP-IV inhibitors unrelated to GLP-1/GLP-1 receptor are an extra and very appreciated value in multi-pathway diseases, such as DRD. The administration route is an issue because although intravitreous injections are used to treat advanced stages of DRD, its use in early stages of DRD is out of place and, therefore, less aggressive approaches should be used. Topical administration of neuroprotective agents by eye drops or other topical delivery systems seems the most appropriate manner to do this. In addition, this allows the self-administration by the patients or their caregivers, thus making unnecessary the intervention of the ophthalmologist.

A transoceanic task force is working not only in improving the understanding of DRD pathogenesis but also in identifying new approaches to clinical assessment (Sun et al., 2021). In this regard, the screening of neurodegeneration/neurodysfunction aimed at identifying those patients in whom neuroprotection should be recommended will change the paradigm of the management of DRD. This strategy will permit us to perform a more personalized and cost-efficient medicine. These words are here particularly relevant because around 30% of patients with diabetes present DRD and we are talking about one of the diseases with a higher economic and societal burden in healthcare systems worldwide.

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