



# ENDOCRINOLOGÍA Y NUTRICIÓN

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## EDITORIAL

### Neurodegeneration as an early event in diabetic retinopathy

### La neurodegeneración como fenómeno temprano en la retinopatía diabética

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Diabetic retinopathy (DR) remains the leading cause of blindness among working-age people in developed countries<sup>1</sup>. Tight control of blood glucose levels and blood pressure is essential for preventing or arresting DR development. However, therapeutic objectives are difficult to achieve and DR therefore occurs in a high proportion of patients. Once DR appears, laser photocoagulation is still the main tool in the therapeutic armamentarium. The aim of laser photocoagulation is not to improve visual acuity, but to stabilize DR, thus preventing severe visual loss. When laser photocoagulation is timely indicated, the 5-year risk of blindness is decreased by 90%, and visual acuity loss is reduced by 50% in patients with macular edema<sup>2</sup>. However, laser photocoagulation is often not timely performed, and its effectiveness in current clinical practice is therefore significantly lower. In addition, laser photocoagulation destroys a part of the healthy retina and side effects such as visual acuity loss, impairment in both dark adaptation and color vision, and visual field loss may thus occur. Intravitreal corticosteroids have successfully been used in eyes with persistent diabetic macular edema and vision loss following failure of conventional treatment. However, reinjections are commonly needed, and there are significant adverse effects such as infection, glaucoma, and cataract

formation<sup>3</sup>. In recent years, intravitreal anti-VEGF (vascular endothelial growth factor) agents have emerged as new treatments for more advanced stages of DR. However, this is an invasive procedure which may cause complications such as endophthalmitis and retinal detachment and may even have deleterious effects on the remaining healthy retina. This is especially important in diabetic patients who may require long-term administration. In addition to local side effects, anti-VEGF agents may also cause systemic complications (e.g. hypertension, proteinuria, renal failure, ischemic cardiovascular disease) because of their capacity to enter systemic circulation. Therefore, specific studies in diabetic patients on the long-term effectiveness and safety of intravitreal anti-VEGF agents are still needed<sup>4,5</sup>. Vitreoretinal surgery may be indicated in advanced DR stages (i.e. vitreous hemorrhage, retinal detachment). However, this therapeutic option requires a skilful team of ophthalmologists, is expensive and fails in more than 30% of cases. In summary, current treatments for DR are applicable at a too advanced stage and are associated with significant adverse effects. Therefore, new drug treatments for the early stages of the disease are needed<sup>3,6</sup>.

DR has traditionally been considered as a microcirculatory disease of the retina due to the harmful metabolic effects of hyperglycemia itself and the metabolic pathways it triggers (polyol pathway, hexosamine pathway, diacylglycerol–protein kinase C pathway, advanced glycation end-products [AGEs], and oxidative stress). However, there is mounting evidence to suggest that retinal neurodegeneration is an early event in pathogenesis of DR

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which antedates and participates in the microcirculatory abnormalities occurring in DR<sup>7-9</sup>. Study of the mechanisms leading to neurodegeneration will therefore be essential for identifying new therapeutic targets in the early stages of DR.

The main features of retinal neurodegeneration (apoptosis and glial activation) have been found in the retina of diabetic donors with no microcirculatory abnormalities in the ophthalmoscopic examinations performed during the year before death<sup>10,11</sup>. Thus, a normal ophthalmoscopic examination does not exclude the possibility that retinal neurodegeneration is already present in the diabetic eye. Neuroretinal damage causes functional abnormalities such as loss of both color discrimination and contrast sensitivity. These changes may be detected by electrophysiological studies in diabetic patients with less than two years of diabetes duration, i.e. before microvascular lesions may be detected by ophthalmological examination<sup>7,12</sup>. In addition, a delayed multifocal ERG implicit time (mfERG-IT) predicts for development of early microvascular abnormalities<sup>13,14</sup>. Furthermore, neuroretinal degeneration will initiate and/or activate several metabolic and signaling pathways which will participate in the microangiopathic process, as well as in disruption of the blood-retinal barrier (a crucial element in pathogenesis of DR).

The end result of retinal neurodegeneration will be loss of neurotransmitters such as dopamine, epinephrine, norepinephrine, acetylcholine, and several neuropeptides, which may play a critical role in development of visual deficits in diabetes. However, rather than focusing on these deficits, it would be more interesting from both the pathophysiological and therapeutic viewpoints to review the main factors accounting for this harmful effect.

Glutamate is the major excitatory neurotransmitter in the retina and is involved in neurotransmission from photoreceptors to bipolar cells and from bipolar cells to ganglion cells. However, increased glutamate levels (resulting in excess stimulation) are implicated in the so-called "excitotoxicity", which leads to neurodegeneration. The excitotoxicity of glutamate results from overactivation of N-methyl-D-aspartate (NMDA) receptors, which have been found to be overexpressed in streptozotocin-induced diabetic rats<sup>15</sup>. There are at least two mechanisms involved in glutamate-induced apoptosis: a caspase-3-dependent pathway and a caspase-independent pathway involving calpain and mitochondrial apoptosis-inducing factor (AIF). Apart from glutamate, there is emerging information on the neurotoxicity induced by angiotensin II in the setting of the renin-angiotensin-system overexpression that exists in DR<sup>3</sup>. In addition, oxidative stress<sup>16</sup> and upregulation of the receptor for AGEs (RAGE) play an essential role in the retinal neurodegeneration induced by diabetes<sup>17</sup>.

In recent years, several peptides with neuroprotective properties such as somatostatin<sup>10,18,19</sup>, cortistatin<sup>20</sup>, and pigment epithelium-derived factor<sup>21</sup> have been found to be downregulated in the diabetic eye, and may therefore play a role in development of retinal neurodegeneration. In addition, the interphotoreceptor retinoid-binding protein (IRBP), a glycoprotein with a major role in the visual cycle and essential for maintenance of photoreceptors, has also been found to be underproduced by the retina in the early stages of DR and to be associated with retinal

neurodegeneration<sup>11</sup>. By contrast, erythropoietin, a glycoprotein with a potent neuroprotective effect, has been found to be upregulated in the retina of diabetic donors in the early stages of DR as compared to non-diabetic donors, and this overexpression was unrelated to mRNA expression in hypoxia-inducible factors (HIF-1 $\alpha$  and HIF- $\beta$ ) from diabetic patients<sup>22,23</sup>. Therefore, stimulating agents other than hypoxia/ischemia are involved in the upregulation of erythropoietin found in the diabetic eye. Based on this, it could be postulated that the capacity of diabetic retina to maintain its neuroprotective factors will be crucial for preventing development of DR.

Based on the foregoing, it would be reasonable to hypothesize that therapeutic strategies based on neuroprotection will be effective for preventing or arresting DR development. In fact, several neuroprotective drugs have successfully been used in experimental models of DR<sup>24</sup>, but clinical trials have not been conducted yet. When early stages of DR are the therapeutic target, it would be inconceivable to recommend an aggressive treatment such as intravitreal injections. To date, eye drop instillation has not been considered as a good administration route for drugs intended to prevent or arrest DR because it is generally assumed that the drug does not reach the posterior chamber of the eye (i.e. the vitreous and retina). However, there is emerging evidence that eye drops are useful in several retinal diseases, including DR<sup>6,25</sup>. This opens up the possibility of developing topical therapy for the early stages of DR, in which the only currently established therapies, intravitreal injections and laser photocoagulation, are too invasive.

From the clinical viewpoint, identification of patients in whom retinal neurodegeneration occurs will open up a new concept in DR screening, and a new scenario in DR treatment based on drugs with neuroprotective effects. This treatment would be able not only to arrest progression of retinal neurodegeneration, but also to prevent development and progression of the early stages of DR (i.e. microaneurysms and/or retinal thickness). Finally, the mechanisms of action mediating the beneficial actions of these drugs should also be investigated. Ophthalmologists, endocrinologists-diabetologists, neurologists, and basic researchers should work together not only in this research, but also in establishing clinical guidelines that will include this new approach to DR management. This coordinated effort would be effective for reducing the burden and improving the clinical outcome of this devastating complication of diabetes.

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