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New Therapeutic Targets in Retinal Disease

K. Thermos

University of Crete, Faculty of Medicine
Department of Basic Sciences, Laboratory of Pharmacology, Heraklion GR-71110, Crete, Greece

SUMMARY

Retinal diseases such as Diabetic Retinopathy (DR) and Age-Related Macular Degeneration (ARMD) lead to vision impairment and blindness. Their global prevalence is increasing due to the rapidly increasing numbers of people with diabetes and older people worldwide, respectively. These diseases are defined as microvascular diseases and characterized by neovascularization. However, neural retinal defects, such as an increase in apoptosis and retinal cell loss, have been detected. These processes are reminiscent of ischemia, glutamate excitotoxicity and neurodegeneration. New pharmacological targets are essential in order to treat both vascular and neural elements of the retina and to provide more efficacious therapeutics for retinal disease.

The neuropeptide somatostatin (somatotropin release inhibitory factor, SRIF) has been shown to have antineovascular actions due to its ability to inhibit the actions of growth hormone, and a variety of other growth factors. We have focused our studies on the elucidation of somatostatin's neuroprotective (anti-ischemic) effects in different models of ischemia induced retinopathies, namely an ex vivo model of chemical ischemia and an in vivo model of AMPA excitotoxicity. Our results support that somatostatin and its $sst_{2/5}$ analogues protect the retina from ischemic insults. The protective effect of the sst_2 ligands was shown to be mediated via a NO/cGMP mechanism. These results, in combination with the increasing literature data on the antineovascular effects of the $sst_{2/5}$ analogues, support the use of these agents as therapeutics in ischemia induced retinal diseases.

Recently, neurosteroids such as dehydroepiandrosterone (DHEA) were shown to have neuroprotective antiapoptotic properties in different paradigms. In addition, these actions were shown to be mediated via a mechanism that involved the NGF pro-survival receptor, TrkA. This evidence provided the impetus for the investigation of the putative neuroprotective actions of DHEA, and synthetic analogues, in retinal models of retinopathies. The endogenous (DHEA) and synthetic androstene neurosteroids employed protected the rat retina from chemical ischemia. In this model, the data suggested that the neuroprotective effects of the neurosteroids are mediated via the NGF receptor and its signaling cascades. In addition, DHEA was shown to protect the retina from AMPA induced excitotoxicity *in vivo*, an effect that was blocked by the TrkA inhibitor and mimicked by NGF itself. These studies are still in preliminary phase, but the present data suggest that neurosteroids may be a new target for retinal therapeutics.

In conclusion, somatostatin analogues and neurosteroids target excitotoxicity and apoptosis in *ex vivo* situations, but most importantly when delivered intravitreally. These properties lend these agents a therapeutic potential in retinal disease, whose pathophysiology involves ischemia induced neurodegeneration. The inclusion of these molecules in a multi drug treatment could ensure a more efficacious therapy.