REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 143 (2010)

The Neurosteroid DHEA Protects the Retina against Chemical Ischemia

P. Giannogonas, N. Mastrodimou, I. Charalampopoulos, A. Gravanis and K. Thermos

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

Key words: Neurosteroids, neuroprotection, ischemia, retina, rat

INTRODUCTION

Ischemia is the underlying cause of many ocular diseases that lead to blindness. Many strategies have been employed to develop therapeutic agents for the successful treatment of ischemia induced retinopathies and the prvention of visual loss. Neurosteroids such as Dehydro-epiandrosterone (DHEA) have recently been shown to have anti-apoptotic properties (1), reminiscent of NGF actions. The aim of the present study was to investigate the putative neuroprotective properties of DHEA, and the involvement of NGF receptor signaling, in a model of retinal chemical ischemia.

METHODS

Eye cups of female Sprague-Dawley rats were incubated with PBS alone or in the presence of iodoacetic acid (5mM) and sodium cyanide (25mM) (Chemical Ischemia Mixture; C.I.M) or C.I.M. and DHEA (10^{-6}, 10^{-8}, 10^{-10} M) for 2x30 min, followed by incubation with PBS or DHEA for 2x30min, at 5%CO_2 / air, 37^{o}C (2). In addition, eye cups were also co-incubated with the chemical ischemia mixture, DHEA (10^{-7} M), and inhibitor of the NGF (TrkA) receptor (10^{-6} M, Calbiochem 648450) or using a mixture of inhibitors - bicuculline/haloperidol/ketamine (all 10^{-6} M) - for GABA/Sigma-1/NMDA receptors, respectively. The eye cups were subsequently fixed and sectioned for PKC, ChAT, and bNOS immunoreactivity, retinal markers for rod bipolar, nitric oxide and cholinergic containing amacrine cells, respectively. TUNEL staining was also employed to examine apoptotic cell loss. In addition, eye cups were lysed and blotted for the detection of phospho- and total-isoforms of prosurvival protein kinases PI3K, Akt, MEK1/2 and ERK1/2.

RESULTS

Chemical ischemia resulted in significant decrease of ChAT, bNOS and PKC immunoreactivities. DHEA (10^{-6}, 10^{-8}, 10^{-10} M) protected the retina in a concentration-dependent manner. The TrkA inhibitor (10^{-6} M) blocked the DHEA (10^{7} M) dependent neuroprotection, whereas bicuculli-ne/haloperidol/ketamine had no effect. In addition, DHEA induced the phosphorylation/active-tion of the kinases examined, strongly indicating that its neuroprotective effects are mediated by these signaling cascades.

CONCLUSIONS

These results demonstrate for the first time that the endogenous neurosteroid DHEA protect the retina from ischemia. In addition, the neuroprotective effects appear to be mediated via the NGF receptor and its signaling cascades. Further studies are essential in order to elucidate the therapeutic relevance of these results.

REFERENCES

1. Charalambopoulos I., et al.: PNAS 2004. *J. Neurochem.* (2008)
2. Mastrodimou N., et al.: Naunyn-Schmied. Arch. *Pharmacol* (2005)