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# DHEA and NGF Protect the Retina from AMPA Excitotoxicity *in vivo*

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## INTRODUCTION

Ischemia has been proposed to play a prominent role in retinal cell death ensuing from several retinal diseases such as glaucoma and diabetic retinopathy. Excitotoxicity, resulting from ischemia, is a pathological process, where increase of glutamate and over activation of glutamate receptors, initiates a cascade of events that lead to visual deficits and blindness. Even today there are no therapeutic agents for the treatment of the neurodegenerative component of retinal diseases. Neurosteroids such as DHEA (Dehydroepiandrosterone) have recently been shown to have antiapoptotic actions via a mechanism involving NGF receptor, TrkA. The aim of the present study was to investigate whether DHEA and NGF could protect retinal cells from cell death in an *in vivo* model of AMPA excitotoxicity.

## METHODS

Intravitreal administration of AMPA (42 nmol per eye) was earlier shown to result in retinal cell loss (ChAT, bNOS and calbindin immunoreactivity (1). The excitotoxicity model was employed in the present study as follows: Male and female Sprague-Dawley rats (250-300 g) were administered: AMPA (42 nmol per eye) or AMPA and DHEA ($10^{-6}$,$10^{-7}$ M) or NGF (60 pg/eye) or vehicle, intravitreally. In addition, a TrkA receptor inhibitor (Calbiochem 648450, $10^{-6}$ M) was co injected with AMPA (42 nmol per eye) and DHEA ($10^{-6}$ M). Twenty four hours after treatment, eye cups were removed and prepared for immunohistochemistry. Antibodies for retinal markers nitric oxide (NO) and cholinergic containing amacrine cells (ChAT-, and bNOS-containing, respectively), and calbindin-containing horizontal and cone bipolar cells, were employed.

## RESULTS

Intravitreal administration of AMPA (42 nmol per eye) led to retinal cell loss as previously reported (1) twenty four hours after administration. Co- administration of AMPA and DHEA protected the retina in a dose dependent manner. In addition, NGF (60pg/eye) mimicked the DHEA effects, thus protecting the retina from AMPA toxicity. The TrkA antagonist ($10^{-6}$ M) employed reversed the neuroprotection afforded to the retina by DHEA ($10^{-6}$M).

## CONCLUSIONS

The present results support that the endogenous neurosteroid DHEA protects the retina from AMPA excitotoxicity via a mechanism involving the TrkA receptor. This was sub-stantiated by the reversal of the DHEA mediated neuroprotection by the TrkA antagonist and by the NGF neuroprotective effects in the retina. Further studies are essential in order to characterize further the down stream signaling events and to evaluate the therapeutic relevance of these results.

1. Kiagiadaki & Thermos: IOVS 49: 3080-3089 (2008)