



Commentary

Transpupillary thermotherapy: New observations on neuroprotection of retinal ganglion cells

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Transpupillary thermotherapy (TTT) is a technique in which heat is delivered to the posterior segment of the eye through the pupil using a modified low power diode laser with a broad beam. This method uses infrared radiation to increase the temperature in the treated tissue up to 10 °C above baseline levels and it is been tried for the treatment of various intraocular tumors and choroidal neovascularization in age-related macular degeneration [7]. However, the bulk of clinical data regarding TTT yields mixed results and further studies are need to demonstrate that improvements in health outcomes occur with acceptable levels of adverse effects.

Recently several neuroscientists using the visual system as a model to study degenerative disorders in the central nervous system (CNS) have turned their attention to the potential possibilities of this technique to treat some retinal neurodegenerative diseases. In CNS it is well establish that in response to physiological, pathological or environmental stress, neurons and glial cells activate the heat shock response in which a set of heat shock proteins (HSPs) are induced, playing important roles in cellular repair and protective mechanisms [1]. It is though that an increase in protein damage can trigger this response, and available studies suggest that HSPs are important in the refolding of partially denatured proteins, the prevention of protein aggregation, the reduction of inflammatory responses and the inhibition of cell death pathways [1–3,6]. These observations point out to HSPs as multifaceted proteins that protect injured neurons from severe damage and allow resumption of normal cellular and physiological activities through a wide variety of mechanisms.

The ability to develop a successful stress response in the face of injury is critical to the long-term viability of individual cells and to the organism in general. The stress response is characterized in part by the upregulation of HSPs and although the mechanism of release remains unknown, it appears that glial cells can release HSPs and that neurons exposed to extra-cellular HSPs are more likely to survive injury than their naïve counterparts [8,9]. In this context the exogenous application of HSPs at neural injury sites could be an effective therapeutic strategy to maintain neuronal viability, which has been tested in several experimental models. For example Yu et al. evaluated the uptake of an intravitreally injected mixture of the 70 kDa heat shock protein Hsc/Hsp70 to prevent photoreceptor phototoxic induced damage and their results showed that Hsc/Hsp70 is taken up by retinal cells and, when administered after an acute injury like light damage, increased the number of surviving photoreceptors [10]. However this approach is clearly invasive and has significant side effects from a clinical point of view. Consequently research on new strategies to induce neuroprotection by non-invasive and safe methods is necessary and it is always welcome.

In this issue Ma et al. present a study linking the neuroprotective effects of TTT on the survival of retinal ganglion cells (RGCs) after significant damage of the optic nerve. Their results confirm and extend previous observations applying a similar methodology [4,5] and suggest that the potential neuroprotective role of infrared laser irradiation could be related to HSPs since Quercetin, an inhibitor of HSPs, abolishes this protective effect. However these results should be treated with caution. Thus transpupillary laser irradiation of the optic nerve head increases RGC density, but it also induces some damage of the optic nerve fibers as well as significant alterations in the chromatin of peripapillary RGCs. Furthermore although the averaged RGC densities between the optic nerve crush group (ONC) and the ONC + TTT group are statistically different at day 7 ($P=0.001$), the results at 14 and 28 days only provide some weak evidence to support that the RGC density is significantly

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higher in the animals undergoing TTT (P values of 0.044 and 0.045, respectively). In addition a recent report using the same approach (optic nerve crush injury model), only found a reduction of RGC loss in retinal areas close to the optic nerve head with borderline significance [5]. Thus the results of Kim et al. show an increase in surviving RGCs from TTT treated eyes at both 7 ($P=0.034$) and 14 days ($P=0.044$) after optic nerve crush injury in retinal areas at 1 mm from the optic nerve head, but no significant differences at bigger distances. These findings suggest that hyperthermia stress induces HSPs upregulation and some neuroprotection on RGC, but also that TTT induced effects could be found only at the treated sites.

These results open the door to further studies on the protective role of HSPs in retinal eye diseases and for future neuroprotective experiments designed to enhance natural cytoprotection. Therefore the manipulation of the cellular stress response may offer novel strategies to protect neuronal cells from damage after acute damage or during the progression of neurodegenerative diseases. Furthermore these preliminary findings could be used to develop new strategies to stimulate mammal adult neurons to use its own cellular repair and protective mechanisms. However we have to be cautious because there are no reported results of the long-term success of this procedure and by now, only TTT seems to provide a moderate, local and temporal neuroprotection.

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