SUMMARY

In the visual system of *Drosophila melanogaster*, heme oxygenase (dHO) has been found to regulate several processes indispensable for stress adaptation and cytoprotection. It has not been specifically explored how dHO influences neurons and glia, where high chances of oxidative challenges may occur regularly. Hence, the present study investigated the role of the gene (*ho*) encoding dHO in the fly's brain under various conditions.

The *ho* mRNA level was shown to follow circadian cycling in the brain under normal conditions with two minima at the beginning of the day and night. After exposure to pro-oxidative conditions (heat stress, and paraquat) and aging, a time-dependent reduction of *ho* mRNA level was detected in the brain. Although for paraquat, *ho* mRNA increased when flies are most active in locomotion. The effects of aging on *ho* expression can be rescued by the chronic supplementation of curcumin (an exogenous antioxidant). It increased *ho* expression and restored its daily rhythmic pattern in older flies. In flies under heat stress, *ho* declined even further after feeding with curcumin. Despite that, curcumin was shown to improve the percentage of survival and climbing performance in flies exposed chronically to high-temperature stress.

Moreover, all conditions studied observed a crosstalk regulation of *ho* expression with apoptosis and autophagy in the fly's brain. Changing *ho* mRNA level in glia did not affect apoptosis under normal conditions, while autophagy was downregulated when *ho* expression was silenced. In neurons, the regulation of apoptosis was shown to be influenced by changes in *ho* mRNA level which varies with the age of flies. On the other hand, the expression of the autophagy-related genes *atg5* and *atg10* was only induced when apoptosis was activated in young flies with *ho* overexpression.

Reducing *ho* transcript level in the fly's brain seemed to be a protective response against oxidative stress. Flies with *ho* silencing in glia survived better after exposure to pro-oxidative conditions, which could be linked to the induction of autophagy. Conversely, the survival of flies with *ho* overexpression was lower under stress, which correlated with a significant reduction of *atg5* mRNA. In addition, promoting excessive *ho* expression in the brain was revealed to adversely affect the living conditions of young flies. Whereas partial suppression of *ho* expression over time enabled aging flies to live longer, especially with curcumin supplementation.

These findings imply that dHO in the fly's brain can be affected by different factors. However, it must be considered that once the *ho* expression level is disrupted, it can affect

neuroprotective and neurotoxic processes, which vary according to *ho* expression level, cell type, and age of flies.