Summary

Promoting retinal ganglion cell survival is pivotal in preventing inner retinal conditions, such as glaucoma. Glaucoma is the leading cause of incurable blindness worldwide, and the increasing numbers of visually impaired individuals are daunting. Although current treatments limit disease progression, they do not cure; Moreover, they do not target retinal ganglion cells. Thus, the need for development of neuroprotective treatment strategies are inevitable.

Retinal ganglion cells are some of the most energy requiring cells of the body, and are metabolically and structurally supported by the Müller cells. Ensuring Müller cell function and inner retinal metabolism is therefore essential in retinal neuroprotection. Taken together with the fact that retinal lactate concentrations exceed any other lactate concentration in the human body, the present thesis aimed to investigate the neuroprotective role of lactate in inner retinal metabolic homeostasis.

The first study of the PhD determined the importance of mitochondrial function in Müller cells during metabolic stress. The second study of the PhD identified lactate metabolism as a crucial component in ensuring Müller cell survival and function. This was induced by being a preferred metabolic substrate in the mitochondria and by enhancing Müller cell function through increased glutamate uptake. The third study of the PhD revealed that activation of the lactate receptor GPR81 increases overall Müller cell metabolism and mitochondrial function, as well as regulating glutamate uptake according to the energetic demand of the cell. The forth study of the PhD put emphasis on a possible lactate shuttle between retinal ganglion cells and Müller cells accentuating lactate pools, which could serve as a spare energy deposit. The neuroprotective effect of lactate was thereby established by rescuing retinal ganglion cells from glucose deprivation through lactate metabolism and ATP production, ultimately securing cellular survival. The fifth study of the PhD identified that patients diagnosed with normal tension glaucoma had lower peripheral lactate levels compared with healthy age-matched controls, implying a possible deficient lactate homeostasis in glaucoma pathophysiology. Also, total blood amino acid levels were lower and unable to be regulated in patients with glaucoma, indicating potential mitochondrial vulnerability in response to metabolic stress mimicked by hypoxia.

In summary, inner retinal metabolic homeostasis plays a pivotal part in maintaining retinal function. Lactate may facilitate these functions by contributing to enhanced Müller cell protection of the retinal ganglion cells, and by being a preferred energy source for the retinal ganglion cells. Further investigations of lactate’s neuroprotective effect in ex vivo and in vivo models are, however, required to unravel potential pharmaceutical targets, ultimately leading to novel therapies in the cure of glaucoma.