Summary

This Thesis discusses the complex topic of the role of proteinase-activated receptors (PARs) in the physiology and pathophysiology of central nervous system diseases, and to some extent, the role of PARs in cancer pathobiology.

Based on the results from this Thesis, we can conclude that PAR2 levels in the CSF do not track neuronal damage; therefore, PAR2 cannot be used as a marker of neuronal damage. Expression and activity of PAR2 in the brain appears to be mostly related to the activity of the disease process itself.

To study the role of PAR2 in neurodegenerative diseases characterized by white matter and oligodendrocyte degeneration, a precise morphological descritption of individual diseases is essential. In the study aimed pathology of motor neuron disease we found reactive increase in oligodendrocyte density in corticospinal tracts in reaction to white matter damage. In other study we confirmed the existence of a new variant of multiple system atrophy, atypical MSA (aMSA) charcterized by specific degenration of hippocampal neurons. Since the activity of kallikrein 6-PAR2 axis attenuates α-synuclein aggregation, its deficiency in hippocampus may be a prerequisite for its dominant degeneration leading to the developmant of α-synuclein neuronal inclusions and aMSA phenotype.

Regarding the degradation of PAR2, we discussed that certain degradation pathways may be shared with PAR2 and other proteins associated with neurodegenerative processes that may share common mechanisms of degradation in endosomal-lysosomal pathway. Therefore, dysfunction of these mechanisms may lead to a pathological accumulation of aggregation--prone, proteins, such as amyloid precursor protein, tau, α-synuclein, or TDP-43. Enhanced PAR2 activity may thus indirectly contribute to disruption of cellular proteostasis.

When evaluating role of PARs in neurodegenerative and other diseases, it is important to consider complex interactions between PARs and proteinases and their inhibitors in both *in vivo* and *in vitro* model systems that are limited by selective use of different methods of PAR activity assessment and of often multifaceted PAR-activity related phenotype.

Only a precise characterization of PARs expression, PARs-associated signaling pathways, organ specific proteinases, and their inhibitors, along with a precise understanding of the structural-functional aspects of the associated diseases will allow for further development of tools to specifically modulate PARs-associated physiological and pathophysiological events. This may eventually lead to a successful treatment for many of serious diseases, mainly neoplastic and inflammatory, which are largely associated with PAR activity.