Biological mechanisms underlying susceptibility to traumatic stress

Summary

This thesis first investigates the role of the *dual specificity phosphatase 22* (*dusp22)* and the entire *dusp* family of genes in mental and neurodegenerative disorders and reviews the available evidence in **Chapter 2**. Given the limited knowledge of the localization and the function of DUSP22 in the brain, this thesis investigates in **Chapter 3** the expression pattern of DUSP22 in mice brain, with a particular focus on the brain regions with an established link to the stress response, i.e., prefrontal cortex, hippocampus, and amygdala.

The *myelin basic protein* (*mbp)* gene also showed different methylation patterns in response to another stressor, i.e., prenatal restraint stress, thereby underscoring the potential importance of differential susceptibility to severe stress. Therefore, this thesis aimed to investigate MBP protein expression profiles in a prime brain region involved in the stress response, i.e., the hippocampus. This thesis includes immunohistochemical analyses in mouse hippocampal subregions and tests whether exposure to social defeat stress was associated with altered MBP protein expression patterns in the mouse hippocampus. This study is in **Chapter 4.**

A third novel candidate gene from the human PTSD study was *myelin transcription factor 1-like* (*myt1l)*, a transcription factor involved in the formation of myelin and the nervous system. Findings from several groups have shown links between *myt1l* and other stress-related mental disorders, spurring us to explore links between *myt1l*, the impact of traumatic stress, and differential susceptibility to traumatic stress. **Chapter 5** describes a study aiming to understand the localization of protein MYT1L in the brain (through immunohistochemical investigation of MYT1L protein expression in the mouse brain) and investigate differences in expression profiles concerning SD exposure.

In order to increase the toolbox to perform experimental studies on the mechanisms mediating or moderating the impact of stress, this thesis includes experiments done using a Microdrive array recording the activity of neural circuitries in the presence of stressful odor presentation. The activity focuses on local field potentials and action potentials in single neuron fire in response to stress *in vivo*. It employs the recently developed construction of Microdrive arrays. **Chapter 6** illustrates the firing pattern in the olfactory neurons of mice in response to predator odor-induced stress, which was recorded by the Microdrive array implanted in the olfaction brain regions of the mice.

The thesis includes experiments using the social defeat stress model to understand the potential role of the identified genes in regulating the short- and long-term impact of exposure to severe stress on behavior, gene expression, and morphology. While doing so, the experiments test the hypothesis that physical activity would be protective (physical activity before stress would reduce the impact of the stress exposure) against the short- and long-term impact of social defeat stress in rodents, which is described in **Chapter 7.**

Chapter 8 summarizes the main research findings and discusses them in light of broader scientific developments.

Chapter 9 provides an outlined summary and future perspectives in rodent models on stress susceptibility.