Glucocorticoid signaling in a rat model of post-traumatic stress disorder

Ding, J.

7

Summary

Samenvatting

List of publications

Curriculum Vitae

Acknowledgements

Summary

Posttraumatic stress disorder (PTSD) is a psychological disorder that develops following exposure to perceived life-threatening trauma. Characteristic features include behavioral changes caused by heightened arousal, including fear and anxiety. PTSD also can cause functional changes in the HPA axis, and in brain regions such as the hippocampus, amygdala and so on. GR hypersensitivity, as defined by strong negative feedback, has been one of the most robust findings of altered HPA axis function in PTSD, but it is unknown whether this GR sensitivity generalizes to the brain. In this thesis, we evaluated GR-related changes in the rat brain that were exposed to the three consecutive stressors of the single prolonged stress (SPS) model for PTSD. We tested the potential of the GR antagonist RU486 treatment in reversing these stress-induced effects, and evaluated the GR sensitivity after administered exogenous corticosterone.

In **chapter 2**, we found that 3 days of GR antagonism had effects on fear behavior, the HPA axis and gene expression in the brain when the antagonist was administered one week after SPS and we subsequently evaluated the effects 15 days after SPS. RU486 had history-independent effects in reducing fear behavior. Gene expression analysis showed a diversity of in- and interdependent effects of stress and RU486. This normalization of a number of SPS effects after RU486 treatment reinforces the potential of targeting GR for treatment of stress-related psychopathologies.

In **chapter 3**, because many studies report behavioral changes one week after SPS, we administered RU486 starting 3 days after SPS exposure and evaluated the effects 8 days after SPS. We compared the treatment with the previously performed intervention at 7 days after SPS and testing after 2 weeks. We demonstrated that the GR antagonist RU486 treatment in the rat acted in interaction with stress, and, again, that it can normalize some stress-induced parameters. However, varying the timing of RU486 administration and evaluation gave different behavioral results and dynamics of gene expression, which revealed complex

interactions between stress and RU486 over time.

In **chapter 4**, we hypothesized that after SPS GR sensitivity is enhanced not only in the HPA axis, but at multiple sites in the brain. We found that at an early time point gene expression of the GR target gene FKBP5 was induced in SPS rats, but not in control rats. Apparently, GR responses were exaggerated, or primed, as a consequence of SPS exposure. Next to sensitization of brain GR signaling that extends beyond direct negative feedback regulation, our data also suggest enhanced stress responsiveness after SPS to moderate but not mild stressors. Increased GR sensitivity may explain the effects of GR antagonists that occur relatively long after stressor exposure.

In **chapter 5**, we hypothesized that intracellular signaling that involves β-arrestin-2, PDE-4 and related signal transduction pathways relates to the fear memory regulation. We evaluated the activity of this pathway in the amygdala in relation to behavior using the SPS model. Our data indicated that SPS caused enhanced fear memory. The changes of β-arrestin-2 and PDE-4 related to fear behavior one week after SPS showed that these factors may be involved in the formation and development of PTSD. We conclude that the SPS lead to a decrease in β-arrestin-2 and a decrease in recruitment of PDE-4 which activates the cAMP-PKA-CREB pathway, and then leading to an enhancement of fear memory.