

Developmental and psychoneuroimmunological mechanisms in depression

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Summary

In this dissertation, we studied the role of inflammation in depression. Concretely, epigenetic changes after prenatal inflammation and the role of the kynurenine pathway in depression were investigated.

First, **Chapter 1** provides an overview of the background of the disease, the current tools used for diagnosis and treatment, and the different pathophysiological theories related to depression. Moreover, the role of epigenetic mechanisms in the link between prenatal infection and depression in the offspring are addressed.

Chapter 2 represents a review about the current literature on how exposure to prenatal maternal infection may interfere with offspring brain development. More specifically, the immune system and the possible involvement of several mediators such as cytokines, neurotransmitters, neurotrophins, hormones and epigenetic processes are reviewed. Moreover, the effects of prenatal maternal stress and infection in the offspring, in view of inflammation, are discussed. Finally, the chapter ends with an overview of sex-differences in response to prenatal maternal infection as well as treatment options for major depression.

Chapter 3 describes the effects of lipopolysaccharide (LPS), an endotoxin contained in bacterial cell walls, on gestational length and intra-uterine and neonatal mortality in mice. The induction of prenatal inflammation using a high dose of LPS significantly decreased gestational length and increased neonatal mortality. When using a low dose of LPS, we observed a tendency

towards reduced litter size. In addition, we discussed the advantages of using subcutaneous injections instead of intraperitoneal injections, when dealing with pregnant animals.

Chapter 4 analyses quinolinic acid (QUIN) in the naïve mouse brain in relation to affect-related behavior. We focused on the localization of QUIN in the naïve mouse because of the lack of knowledge regarding QUIN in healthy, control conditions. We showed QUIN-immunoreactivity particularly in the cingulate cortex (CC) delineating individual cells and in the thalamic reticular nucleus (TRN) resembling a fibrillary staining pattern. Moreover, we observed a strong correlation between QUIN-immunoreactivity in the TRN and motor activity in the open field test, suggesting a role of QUIN in the regulation of motor activity in normal conditions.

In **Chapter 5** we assessed alterations in epigenetic mechanisms in the mouse brain after prenatal exposure to polyinosinic:polycytidylic acid (Poly I:C). More specifically, we examined global histone deacetylase (HDAC) and DNA methyltransferase (DNMT) activity within the brain. We found a significant sex x treatment interaction effect after prenatal exposure to maternal immune challenge by Poly I:C, indicative of increased global HDAC activity particularly in female offspring from mothers injected with Poly I:C when compared to controls. In addition, the levels of the isoforms HDAC 1,2,3,4 and 6 were explored as a possible explanation for the increase observed in global HDAC activity. However, we could not detect significant higher levels of the HDAC isoforms examined in Poly I:C versus control female offspring.

Although we observed a treatment effect with increased HDAC6 in offspring of mice treated with Poly I:C compared to controls, this effect seemed to be more pronounced in male - and not female - offspring, which does not match the global HDAC activity data. A feasible explanation for the discrepancy observed between the global HDAC activity and the protein levels of several HDAC isoforms in the present study is that one or more other HDAC isoform(s) than those assessed using western blotting is/are involved in mediating the observed increased in global HDAC activity. Taken together, this study indicates that prenatal maternal Poly I:C exposure seems to increase global HDAC, but not DNMT activity, particularly in female offspring. Altogether, though purely speculative, these data suggests a role for HDAC6 in mediating the association between prenatal maternal infection and the development of depression in the offspring.

Chapter 6 investigates alterations in the depression scores and in diverse enzymes and metabolites of the kynurenine pathway in Interferon-alpha (IFN- α) treated patients. We report a significant change over time in both the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI) scores during IFN- α therapy. In addition, levels of the neurotoxic metabolite kynurenine (KYN), 3-hydroxykynurenine (3HK), quinolinic acid (QUIN) and the kynurenine/tryptophan (KYN/TRP) ratio were increased over time, while the kynurenic acid/kynurenine (KYNA/KYN) ratio, reflecting neuroprotective properties, was reduced. Regarding the enzymes of the kynurenine pathway, the activity of kynureninase (KYNase), kynurenine-3-monooxygenase (KMO) and kynurenine aminotransferase

(KAT-3) were also increased. When examining the relationship between MADRS scores and metabolites, KYNA and the KYNA/KYN ratio were negatively associated with MADRS scores. On the other hand, no association was observed between enzymes and the MADRS score. Finally, relative expression of KYNase significantly predicted levels of 3HK. Altogether, our results confirm, that the kynurenine pathway plays an important role in the development of depressive symptoms during IFN- α treatment, with a shift in the balance between neurotoxic and neuroprotective metabolites, as well as increased expression of enzymes regulating the neurotoxic arm of the pathway.

Finally, in **Chapter 7**, a summary and discussion of the main findings of this thesis are provided. In addition, some methodological considerations are addressed. Finally, concluding remarks are disclosed.

To sum up, in this thesis, we investigated possible mediators of the effects produced during brain development in offspring after prenatal inflammation, such as epigenetic mechanisms. In addition, we explored the role of QUIN in healthy conditions. Finally, we examined the role of several enzymes and metabolites of the kynurenine pathway in relation to depression in IFN- α treated patients. To conclude, we showed that prenatal maternal inflammation mediated changes in epigenetic marks, while exposure to cytokines in adulthood affected the kynurenine metabolism in relation to depression.