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Streszczenie w języku angielskim rozprawy doktorskiej mgr inż. Anna Solarz-Andrzejewskiej pt. „ The role of the blood-brain barrier, inflammation and endoplasmic reticulum stress in the mechanisms of susceptibility and resilience to early-life stress”

Clinical data indicate that early-life stress (ELS) may increase the risk of physical and mental health problems later in life. The above-mentioned health conditions include particularly depression, anxiety disorders, cognitive impairments, as well as, a metabolic syndrome. The common thread in etiology and progression of these disorders can be disturbances in the inflammatory processes, blood-brain barrier (BBB) function and proteostasis.

Despite the expanding knowledge about the impact of ELS on brain maturation and function, the mechanisms underlying the susceptibility or resilience to its effects remain insufficiently understood. The present doctoral dissertation was aimed to broaden the knowledge in this subject, particularly in terms of the engagement of the BBB, neuroinflammation and cellular stress in the biology of ELS, modeled by the maternal separation (MS) paradigm in rats.

First, the effects of MS on the BBB maturation and integrity was studied in both sexes at different developmental stages. The second goal was to examine whether MS determines the subsequent inflammatory response induced by acute lipopolysaccharide (LPS) administration. In the next part of the doctoral dissertation, the involvement of cellular stress in the mechanisms of susceptibility or resilience to ELS was investigated.
In this regards, the impact of MS on the expression of 70-kDa heat shock proteins (HSP70), endoplasmic reticulum (ER) stress and unfolded protein response (UPR) markers in the brain were analyzed. Finally, repeated early-life administration of ER stress inhibitor, salubrinal (SAL), was used to assess the involvement of this process in MS-induced dysfunction of the medial prefrontal cortex (mPFC) maturation and rat behavior.

The studies revealed developmental and sex differences in BBB functioning in rats in basal conditions and under an inflammation. Developmental sealing of the BBB was observed and sex differences in BBB permeability and integrity. Additionally, MS did not have a clear negative impact on many of the studied BBB permeability- and homeostasis-related parameters, and observed effects were age-, brain region- and sex-dependent. Nevertheless, juvenile males were more sensitive to ELS.

Next, the research showed that MS in a sex-dependent manner modulated LPS-induced neuroinflammatory response. In juvenile males subjected to MS, this response was enhanced, while in females, not changed by MS or even blunted, especially in adulthood.

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The subsequent studies revealed a long lasting overexpression of HSPA1B and HSPA5 in the blood and brain with concomitant impairments in synaptic plasticity and reduced anxiety in adult males subjected to MS. Based on these findings, HSP70 family members were proposed as potential candidates for ELS biomarkers.

Analysis of the expression of ER stress, UPR and apoptosis markers in the mPFC did not show a strong impact of MS at the studied developmental stages. Nevertheless, SAL and/or its vehicle administration prevented or blunted some of the MS effects at biochemical and behavioral levels.

The results indicate that the regulation of BBB function, inflammatory processes and cellular stress responses during brain maturation may play an important role in the mechanisms of susceptibility or resilience to ELS. Moreover, they highlight the need to expand the research to multiorgan approach to better understand the complex effects of ELS on mental and physical health and to find universal biomarkers facilitating diagnostics for ELS-related diseases.

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