Abstract

Current treatments of the neurodevelopmental disorder schizophrenia are mainly targeted against the positive symptoms of the disorder. The treatment of cognitive symptoms, however, is still an unmet need. Moreover, the underlying mechanisms of how these symptoms develop are not fully understood. Recent literature suggests an involvement of redox imbalance, myelin deficits and oligodendrocyte abnormalities in this process. Our hypothesis poses that a redox imbalance might lead to stress in oligodendrocytes and myelin deficits, with subsequent cognitive symptoms. We used the APO-SUS rat line as a model for schizophrenia, with the APO-UNSUS counterpart animals as controls. We investigated whether deficits in redox-related gene, myelin-associated protein and oligodendrocyte transcription factor mRNA expression are present in several brain regions of female APO-SUS rats of pre- and post-adolescent ages. In medial prefrontal cortex and the dorsal striatum of female APO-SUS, myelin- associated protein mRNAs were down-regulated at several ages. Also at these ages, mRNAs of two redox-related genes, Gstm4 and Prdx6, showed dysregulated expression. Furthermore, the presence of cognitive deficits in the executive functioning domain was evaluated by a perceptual discrimination paradigm and the possibility for consequent remyelination was explored at the transcript level in APO-SUS and APO-UNSUS males. We found that male APO-SUS showed lower performance and faster inter-trial intervals after an intra-dimensional shift in the perceptual discrimination paradigm. However, no increase in mRNA expression of myelin-associated proteins in the medial prefrontal cortex was observed after extensive neuronal activation. Lastly, myelin deficits at different developmental time-points were investigated at the structural level in male APO-SUS by Third Harmonics Generation Microscopy validated by immunohistochemistry. Third Harmonics Generation microscopy showed differences in third harmonic signal contrast between male APO-SUS and their APO-UNSUS counterparts, and was able to visualize the developmental event of myelination. Summarizing, the present study clearly suggests a link between redox imbalance and oligodendrocyte and myelin deficits. Further studies into this hypothesis are necessary to aid in the development of remyelination strategies that could ultimately alleviate cognitive symptoms in patients with schizophrenia

Keywords

schizophrenia, myelin, redox, APO-SUS, oligodendrocyte, medial prefrontal cortex, dorsal striatum, sex difference, cognitive symptoms, remyelination, Third Harmonics Generation microscopy, mRNA expression