The temporal profiles of frontal gene expression compared in the rat model of post-traumatic stress disorder (PTSD) and the conditioned fear model

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Background

Post-traumatic stress disorder (PTSD) is a stress-related disorder, which may occur after experiencing life-threatening events. The abnormal fears in PTSD which are different from the learned fear with resilience to extinction, impaired fear extinction and fear exaggeration are two crucial factors for the maintenance of PTSD. The prefrontal cortex (mPFC) is considered a key region of top-down control in fear regulation, and gene alternation after traumatic stress exposure has been indicated closely related to the pathological state of PTSD. However, the temporal genetic alternations from the early phase to the late phase after traumatic stress exposure still remain unclear, especially in the critical brain area–the mPFC.

Aims & Objectives

In this study, with the observation from the rat models, we hypothesize that after traumatic stress exposure, the frontal gene expression patterns could be reflected by early and late phases, and with the comparison of the fear rat model, genetic features of abnormal fears could be further characterized in the PTSD rat model.

Methods

Here, we use a well-established modified single-prolonged stress (SPS&FS) PTSD rat model and a fear conditioning model (FS model); the frontal tissue was collected after traumatic stress exposure or fear conditioning, RNA was extracted and later subjected to transcriptome-level gene sequencing. The genetic profiling of the mPFC at early (<2hr post SPS&FS or FS exposure) and late (D7 post SPS&FS or FS exposure) stages were compared by principal component analysis (PCA), gene function and regulatory network analysis in these two models.

Results

First, we identified temporal alternations in these two models and found pathways such as EIF2, NRF2-mediated oxidative stress response and acute phase responding signaling were enriched in the early state in both PTSD and fear conditioning models with significant p-values. Second, in the late stage, the sirtuin signaling pathway was found significant in both models; other pathways such as STAT3, cAMP, lipid metabolism, Gα signaling, and increased fear were found particularly enriched in the late stage of the PTSD model. However, other pathways such as VDR/RXR, GP6 and PPAR signaling were found significant in the late stage of the FS model. Last, genes in the network of psychological disorder, endocrine system and increased fear show distinguished temporal patterns in the PTSD and FS models.

Discussion & Conclusion

The genetic profiling of the frontal region in the early and late stages of PTSD and FS models could help elucidate the biological progression after traumatic stress exposure or fear conditioning; besides, the modeling of traumatic stress exposure in animal models, helps further investigation of the early stage after traumatic stress exposure, and which is a difficult stage to be observed in clinical. Understanding the temporal alternation could help identify stage-specific pathways and also differentiate the pathological condition of PTSD from the non-pathological condition of learned fears.

Keywords:
Post-traumatic stress disorder, fear conditioning, temporal gene profiling, the prefrontal cortex and gene network.