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HIF-1A AND HIF-2A ARE UPREGULATED IN THE HIPPOCAMPUS BUT NOT IN THE MEDIAL PREFRONTAL CORTEX IN EXPERIMENTAL PTSD

Background. Post-traumatic stress disorder (PTSD) is characterised by anxiety, maladaptive stress responses, and memory disturbances. Hypoxia-inducible factors (HIFs) are transcriptional regulators involved in metabolic adaptation and BDNF signalling – processes implicated in PTSD pathophysiology. Our study aimed to characterise behavioural and region-specific molecular alterations in a rat model of PTSD, focusing on the HIF-1a, HIF-2a, HIF-3a, PACAP, and PAI-1 expression in the hippocampus and medial prefrontal cortex (mPFC). **Methods.** PTSD was modelled in adult male outbred rats ($n = 18$ PTSD, $n = 24$ control) using the SPS protocol: 2-hour immobilisation, 15-minute forced swimming, and diethyl ether anaesthesia, followed by a 7-day incubation period. Behavioural assessment employed the Open Field Test, Elevated Plus Maze (EPM), and Dark-Light Box. Gene expression in the hippocampus and cerebral cortex was quantified by RT-qPCR using β -actin as a reference gene. **Results.** SPS-exposed rats exhibited a robust anxiety-like phenotype in the EPM: freezing time was nearly three times higher in PTSD animals than controls (31.6 vs 12.8 s; $p < 0.001$), freezing episodes were twice as frequent (7.9 vs 4.2; $p < 0.01$), open arm time was reduced (26.2 vs 54.2 s; $p < 0.05$), open-arm head dips decreased (11.5 vs 19.9; $p < 0.01$), and total distance travelled was lower (0.66 vs 0.90 m; $p < 0.05$). Dark-Light Box confirmed avoidance behaviour: light zone entries were significantly reduced in PTSD animals (1.3 vs 2.3; $p < 0.01$). No significant group differences were detected in the Open Field Test. At the molecular level, hippocampal HIF-1a expression was more than doubled in PTSD animals relative to controls (6.41 vs 3.12 relative units; $p = 0.028$), and HIF-2a was elevated approximately 2.2-fold (57.7 vs 26.4 relative units; $p = 0.036$). No significant changes were found for HIF-3a, PACAP, or PAI-1 in either region, nor for any target in the mPFC. **Conclusions.** SPS reliably induces a PTSD-like behavioural phenotype and is accompanied by selective upregulation of HIF-1a and HIF-2a in the hippocampus – a finding not previously reported in this model. The absence of corresponding cortical changes identifies the hippocampus as one of the key regions showing hypoxia-inducible pathway activation under chronic psychological stress, while other PTSD-relevant structures (e.g., amygdala, nucleus accumbens, hypothalamus) remain to be examined. These findings are based on transcript-level data; protein-level validation is ongoing. These findings support investigation of HIF-dependent signalling as a component of PTSD molecular pathophysiology.

Keywords: PTSD, Single Prolonged Stress, hypoxia-inducible factors, HIF-1a, HIF-2a, hippocampus, rat model

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