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CHRONIC PSYCHOSOCIAL STRESS IN MICE CAUSES NEURO-IMMUNE-MONOAMINE CHANGES IN BRAIN AND DEPRESSION-RELEVANT BEHAVIOUR THAT IS REVERSIBLE BY ANTI-INFLAMMATORY TREATMENT

C. Pryce[1], D. Azzinnari[1], H. Sigrist[1], E. Seifritz[1], R. Fuertig[2], A. Ceci[2], B. Hengerer[2]

[1]Psychiatric Hospital, University of Zurich, Zurich, Switzerland ; [2]CNS Research, Boehringer Ingelheim, Biberach, Germany

Introduction: Valid animal models are essential to understanding the aetio-pathophysiology of depression psychopathology and therefore its pharmacological treatment.
Aims: To establish a mouse model with aetiological and face validity, investigate the mediating pathophysiology, and the effects of reference anti-depressants and novel-target pharmacology.
Methods: Adult male C57BL/6 mice were exposed to chronic social defeat (CSD) in the form of 15-day distal exposure to, and 1-min daily attack without wounding by, dominant CD-1 mice. Behavioural effects were studied in terms of changes in fear conditioning, generalized helplessness and fatigue. Physiological effects were studied in terms of in plasma levels of pro-inflammatory cytokines and tryptophan catabolites. CNS transcriptome-level effects were studied in terms of de-regulated gene expression in hippocampus, amygdala and medial prefrontal cortex. Pharmacological reversal of CSD behavioural effects were studied using escitalopram and an indoleamine 2,3-dioxygenase (IDO) inhibitor.

Results: Relative to controls, CSD mice exhibited increased acquisition and expression of fear conditioning to CS and context, increased generalized helplessness in terms of 2-way escape failure, and increased fatigue on a 1-way escape-avoidance treadmill. CSD mice exhibited increased plasma levels of TNF and IL-6, increased tryptophan catabolites and decreased serotonin, and splenomegaly. CSD mice exhibited de-regulation of immune-inflammation genes in hippocampus and of dopamine and serotonin genes in amygdala. CSD-induced behavioural dysfunction was moderately reversed by escitalopram and more robustly reversed by an IDO inhibitor.

Conclusion: This valid mouse model provides comprehensive evidence for immune-inflammation – monoamine aetio-pathophysiology of depression and the therapeutic importance of targeting this pathway in novel anti-depressant treatment strategies.

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