

CONSTRUCT AND FACE VALIDITY OF A NEW MODEL FOR THE THREE-HIT THEORY OF DEPRESSION USING PACAP MUTANT MICE ON CD1 BACKGROUND

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Abstract—Major depression is a common cause of chronic disability. Despite decades of efforts, no equivocally accepted animal model is available for studying depression. We tested the validity of a new model based on the three-hit concept of vulnerability and resilience. Genetic predisposition (hit 1, mutation of pituitary adenylate cyclase-activating polypeptide, PACAP gene), early-life adversity (hit 2, 180-min maternal deprivation, MD180) and chronic variable mild stress (hit 3, CVMS) were combined. Physical, endocrinological, behavioral and functional morphological tools were used to validate the model. Body- and adrenal

weight changes as well as corticosterone titers proved that CVMS was effective. Forced swim test indicated increased depression in CVMS PACAP heterozygous (Hz) mice with MD180 history, accompanied by elevated anxiety level in marble burying test. Corticotropin-releasing factor neurons in the oval division of the bed nucleus of the stria terminalis showed increased FosB expression, which was refractive to CVMS exposure in wild-type and Hz mice. Urocortin1 neurons became over-active in CVMS-exposed PACAP knock out (KO) mice with MD180 history, suggesting the contribution of centrally projecting Edinger–Westphal nucleus to the reduced depression and anxiety level of stressed KO mice. Serotonergic neurons of the dorsal raphe nucleus lost their adaptation ability to CVMS in MD180 mice. In conclusion, the construct and face validity criteria suggest that MD180 PACAP HZ mice on CD1 background upon CVMS may be used as a reliable model for the three-hit theory. © 2017 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: maternal deprivation, chronic variable mild stress, CRF, Urocortin1, serotonin, FosB.

INTRODUCTION

Major depression is a mood disorder affecting 350 million people globally. This stress-related mental condition has a substantial impairing effect on various fields of the patient's life resulting sometimes in suicide (WHO, 2016). Despite the severity we still lack a deeper understanding of etiology, pathomechanism and a reliable therapy. For instance, opposing clinical phenomena (i.e. weight loss vs. gain, insomnia vs. hypersomnia) (for details see reference: Diagnostic and Statistical Manual of Mental Disorders-5 2013) support the diagnosis of human major depressive disorder. This suggests that the entity of major depressive disorder harbors conditions of heterogeneous neurobiological mechanisms (for review see Kormos and Gaszner, 2013; Farkas et al., 2016). At therapeutic level, anti-depressant drugs, acting on monoaminergic systems, proved to be ineffective in about 30% of the cases (Catena-Dell'Osso, 2013). These observations demonstrate that beyond monoaminergic systems other neural circuits are also involved and the discovery of new, more reliable animal models is imperative. Extended studies on multiple stress adaptation centers would also accelerate the search for potential drug targets (Kormos and Gaszner, 2013; Farkas et al., 2016).

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Abbreviations: 5-HT, serotonin; ACTH, adrenocorticotropin; AFR, animal facility rearing; BSTov, oval division of bed nucleus of stria terminalis; CeA, central nucleus of amygdala; CORT, corticosterone; cpEW, centrally projecting Edinger–Westphal nucleus; CRF, corticotropin-releasing factor; CTRL, control; CVMS, chronic variable mild stress; DR, dorsal raphe nucleus; EDTA, ethylene-diamine tetra-acetic acid; FST, forced swim test; HPA, hypothalamus–pituitary–adrenal; HZ, heterozygous; KO, knock out; LDB, lightdark box; MANOVA, multifactorial analysis of variance; MBT, marble burying test; MD180, maternal deprivation (180 min long); MS15, maternal separation (15 min long); NDS, normal donkey serum; PACAP, pituitary adenylate cyclase-activating polypeptide; PBS, phosphate-buffered saline; PD, postnatal day; PVN, paraventricular nucleus; SSD, specific signal density; TST, tail suspension test; Ucn1, urocortin 1; WT, wild type.

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