Disclosure statement:
This work was supported by the ÚNKP-22-3 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund.

doi: https://doi.org/10.1016/j.nsa.2023.102595

P.0805
NEUROSCIENCE APPLIED 2 (2023) 102441 102596
DYSREGULATION OF BDNF AND PI3K/AKT SIGNALING IN THE BRAIN OF FEMALE WISTAR-KYOTO RATS EXPOSED TO CHRONIC MILD STRESS

K. Virijević [1], N. Spasojević [1], B. Stefanović [1], H. Ferizović [1], M. Janković [1], S. Dronjak [1]. [1] *Institute of Nuclear Sciences "Vinca", Laboratory of Molecular Biology and Endocrinology- University of Belgrade, Belgrade, Serbia*

Background: The neurobiology underlying depression has not yet been fully identified, but is thought to result from molecular and cellular abnormalities that interact with genetic and environmental factors. Depression is twice as prevalent in women as in men, however, females remain underrepresented in preclinical research. In addition to the neurotransmission theory of depression, the inflammatory processes and the disrupted signaling pathways also play a crucial role in the pathophysiology of depression. The WKY rat strain has long been established as a model of depression. These rats demonstrate an exaggerated response to stress compared to other strains. WKY strain fail to respond to chronic antidepressant treatment after exposure to chronic mild stress (CMS) and considered to be nonresponsive to antidepressant drugs. The hippocampus and the medial prefrontal cortex (mPFC) are thought to be an important regions for depression. Brain-derived neurotrophic factor (BDNF) play a vital role in the pathophysiology of depression. BDNF-stimulated signaling cascades, including the phosphatidylinositol 3-kinase (PI3K)–/serine threonine kinase (Akt), also implicated in depression and treatment respons. In the present study, we have examined the effects of CMS on behavior and BDNF and PI3K/Akt signaling in the hippocampus and mPFC of female WKY rats.
Method: In the experiment, we used three months old Wistar (WI) and WKY female rats. Animals were divided in two groups: control and animals exposed to CMS for 6 weeks. On the last day of stress procedure, animals were tested in elevated plus maze to determine the levels of anxiety. Animals were then sacrificed and hippocampus and mPFC were isolated. Levels of BDNF and pAkt were determined by Western blot method. Data were analyzed using the two way ANOVA and Tuckey's post-hoc test.
Results: WKY rats showed significantly decreased number of rearings (by 70%, $p<0.01$),decreased number of total arm entries (by 21%, $p<0.05$) and the time spent in the open arms (by 73%, $p<0.001$) of the elevated plus-maze compared to WI control group. WKY females had a significantly lower level of BDNF in the hippocampus (by 12%, $p<0.05$) and mPFC (by 16%, $p<0.05$) and pAkt (by 14%, $p<0.01$) only in mPFC as compared to the WI female rats. Exposure of WKY females to CMS enhanced an anxiety-like behavior and hypolomotion (decrease in number of rearings by 31%, $p<0.05$, number of total arm entries by 89%, $p<0.001$, and timevspent in the open arms by 92%, $p<0.001$), further down-expression of BDNF in both brain areas (in PFC: by 15%, $p<0.001$; in hippocampus: by 7%, $p<0.05$) and Akt phosphorylation in the mPFC (by 17%, $p<0.05$) as well as a decreased pAkt in the hippocampus (by 36%, $p<0.001$).
Conclusions: The difference in the balance of BDNF and PI3K/Akt signaling pathways may be relevant to the resistance of WKY rats to antidepressant drug treatment and may be useful for developing new targets for depression treatment, especially in females.
No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2023.102596

P.0806
NEUROSCIENCE APPLIED 2 (2023) 102441 102597
HISTAMINERGIC NEURONAL PATHWAYS UNDERLIE SUSCEPTIBILITY AND RESILIENCE TO PSYCHOSOCIAL STRESS

A. Costa [1], G. Provensi [1], R. Leurs [2], P. Blandina [3], B. Passani [4]. [1] *University of Florence, Dept. of Neuroscience- Psychology- Drug Research and Child Health, Firenze, Italy;* [2] *Vrije Universiteit Amsterdam, Faculty of Science- Medicinal chemistry, Amsterdam, Netherlands;* [3] *University of Florence, Neuroscience-Psychology- Drug Research and Child Health-, Firenze, Italy;* [4] *University of Florence Italy, Health Sciences, Florence, Italy*

Psychosocial stress is considered a severe pathogenic factor of psychiatric disorders, characterized by dysfunctions of cognitive, emotional, and social domains. Not everyone though, who experiences an adverse or stressful event succumbs to negative outcomes and enters a pathological state, as some individuals are highly vulnerable to the pathological consequences of enduring stress, whereas others are resilient. We and others previously showed that manipulation of histaminergic neurons of the hypothalamic tuberomamillary nucleus (TMN^{HA}) impacts on the instatement of a specific stress-induced phenotype [1,2].
Aims This study aims at understanding the implications of hypothalamic histaminergic nuclei in the unfolding of maladaptive behavioural responses to stress. In particular, we asked whether TMN^{HA} neurons are engaged in the initial or more durable resilience/susceptibility responses to enduring stress in a preclinical setting.
Methods To disentangle the involvement of the TMN^{HA} neurons in stress susceptibility and resilience, chemogenetic, genetic and pharmacological manipulations techniques were used in the murine model of social defeat stress (SDS), consisting of daily exposure of the experimental animal to an aggressive conspecific for variable periods of time. Animals a) Histidine decarboxylase (HDC)cre male mice subjected to CNO-mediated activation or inhibition of TMN^{HA} neurons via bilateral intra-TMN viral injection of either AAV8-hSyn-DIO-hM3D(Gq)-mCherry or AAV8-hSyn-DIO-hM4D(Gi)-mCherry constructs, respectively; b) $HDC^{-/-}$ mice; c) $HDC^{+/+}$ mice pharmacologically depleted of brain histamine with injections of the HDC inhibitor alpha-fluoromethylhistidine (a-FMH; 1µg/ml, 5µl i.c.v. [3]); d) $HDC^{+/+}$ mice treated with pitolisant (10mg/Kg i.p. [3,4] or VUF16839 (5mg/Kg i.p. [5]), histamine H_3 receptor antagonist and agonist, respectively; mice receiving AAV8-hSyn-DIO-mCherry and non-stressed mice served as controls. Mice performance was then evaluated in paradigms relevant to social (social interaction test) and cognitive (novel object recognition test) domains. Statistical analysis: 2WayANOVA & Bonferroni MCT; significance $p<0.05$. N of animals = 6-9/experimental group.
Results Exposure to 10 day-SDS induced social avoidance and poor recognition memory in control mice. Chemogenetic, and pharmacological activation of TMN^{HA} neurons with the H_3 receptor antagonist pitolisant significantly improved the social interaction index (P range <0.05-0.001 between groups) and recognition memory (P range <0.01-0.001 between objects). On the other hand, chemogenetic silencing of TMN^{HA} neurons during a 3-day SDS, which normally does **not** induce maladaptive responses, caused social avoidance (P range <0.05-0.001 between groups) and recognition memory deficits (P range <0.05-0.0001 between objects). Similar susceptibility to a subthreshold SDS protocol was observed in $HDC^{-/-}$ mice, mice receiving alpha-FMH, or VUF16839.
Conclusions These results indicate the full implication of the brain histaminergic system in promoting a coping behaviour toward stress-related dysfunctions. By using different experimental manipulations we show that global activation of histaminergic neurons promotes resilience to SDS-induced behavioural alterations, whereas their silencing triggers susceptibility. These results indicate that pharmacological interventions targeting the histaminergic system as with pitolisant, an effective compound for the treatment of narcolepsy, can promote coping resilience and ultimately normalize the affected systems.
References
1.Rani, B., Santangelo, A., Romano, A., Koczwara, J.B., Friuli M., Provensi G., et al. 2021 Brain histamine and oleoylethanolamide restore behavioral deficits induced by chronic social defeat stress in mice Neurobiol Stress 14:100317. doi: 10.1016/j.ynstr.2021.100317. eCollection 2021 May. 2.Endou, M., Yanai, K., Sakurai, E., Fukudo, S., Hongo, M., Watanabe, T. 2001 Food-deprived activity stress decreased the activity of the histaminergic neuron system in rats Brain Res. 891:32-41. 3.Brabant C, Charlier Y, Tirelli E (2013) The histamine H3-receptor inverse agonist pitolisant improves fear memory in mice. Behav Brain Res 243:199–204. 4.Krief, S., Berrebi-Bertrand, I., Nagmar, I., Giret, M., Belliard, S., Perrin, D., et al. 2021 Pitolisant, a wake-promoting agent devoid of psychostimulant properties: Preclinical comparison with amphetamine, modafinil, and solriamfetol. Pharmacol Res Perspect 9(5):e00855. doi: 10.1002/prp2.855. 5.Rani, B., Silva-Marques, B., Leurs, R., Passani, M.B., Blandina, P., Provensi, G. 2021 Short- and Long-Term Social Recognition Memory Are Differentially Modulated by Neuronal Histamine Biomolecules. 11(4):555. doi: 10.3390/biom11040555
No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2023.102597