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## P.0805

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## DYSREGULATION OF BDNF AND PI3K/AKT SIGNALING IN THE BRAIN OF FEMALE WISTAR-KYOTO RATS EXPOSED TO CHRONIC MILD STRESS

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**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 responses. 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 Tukey'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 hypolocomotion (decrease in number of rearings by 31%,  $p < 0.05$ , number of total arm entries by 89%,  $p < 0.001$ , and time spent 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

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## HISTAMINERGIC NEURONAL PATHWAYS UNDERLIE SUSCEPTIBILITY AND RESILIENCE TO PSYCHOSOCIAL STRESS

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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 tuberomammillary nucleus (TMN<sup>HA</sup>) 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<sup>HA</sup> 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<sup>HA</sup> 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<sup>HA</sup> 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<sup>-/-</sup> mice; c) HDC<sup>+/+</sup> mice pharmacologically depleted of brain histamine with injections of the HDC inhibitor alpha-fluoromethylhistidine (α-FMH; 1 μg/ml, 5ul i.c.v. [3]); d) HDC<sup>+/+</sup> mice treated with pitolisant (10mg/Kg i.p. [3,4] or VUF16839 (5mg/Kg i.p. [5]), histamine H<sub>3</sub> 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<sup>HA</sup> neurons with the H<sub>3</sub> 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<sup>HA</sup> 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<sup>-/-</sup> mice, mice receiving α-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.

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