DOI 10.18699/BGRSSB-2018-192

Lethal yellow (A^Y) mutation in the *agouti* gene causes the depressive-like alterations in the mouse brain and behavior

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Key words: lethal yellow, brain, behavior, MRI, mice, depressive-like alterations

Motivation and Aim: The *agouti* gene is expressed only in cells of the hair follicle and it induces yellow pigment (phaeomelanine) synthesis by melanocytes [1]. The lethal yellow (A^Y) mutation results from the large deletion in the promotor of the mouse agouti gene that put the agouti gene under control of the promotor of a ubiquitously expressed Raly gene. In addition, A^Y mutation causes ectopic expression of the agouti protein in many tissues including the brain, adipose and other tissues. The agouti protein is an inhibitor of the melanocortin-4 receptors involving in the regulation of total metabolism and feeding behavior. So, A^Y mutation causes obesity and diabetes II alteration in mice [2]. The aim of this study is the effect of the A^Y mutation on the brain and behavior.
Methods and Algorithms: The experiments were carried out on adult (11–12 weeks old) males of A^Y/a mice and their wild-type counterparts (*a/a*).
Results: Mice of A^Y/a and *a/a* genotypes did not differ in their home cage activity, sleep, food and water consumption, learning ability in the Morris water maze, anxiety in the open field and elevated plus-maze, as well as in the level and metabolism of monoamines and expression of some proinflammatory genes in the brain. At the same time, A^Y/a showed elevated fat mass ($F_{1.14} = 46.3$, $p < 0.0001$) and depressive-like behavior in the forced swim test ($F_{1.14} = 11.85$, $p < 0.01$) compared with *a/a* mice. MRI revealed a reduction of cortex volume ($F_{1.14} = 13.65$, $p < 0.01$), while MR spectroscopy showed a shift the balance between excitatory and inhibitory substances to excitatory substances in the hippocampus in A^Y/a mice. The level of mRNA of *Ptpn5* gene encoding striatal enriched protein tyrosine phosphatase in the frontal cortex of A^Y/a mice was elevated compared with their wild-type counterparts ($F_{1.13} = 10.71$, $p < 0.01$).
Conclusion: In the present study we first investigate the effects of A^Y mutation on the mouse brain and behavior. So, the A^Y mutation precipitated depressive-like alterations in the behavior and brain functions and A^Y/a mice are a promising model of depressive disorders induce by metabolic dysfunction.
Acknowledgements: Supported by the RSF (grant No. 17-15-01032) with using of equipment of the Research Center supported by the Russian Ministery of Education and Science (project No. RFMEFI62117X0015). The maintenance of mice was supported by the basic research project No. 0324-2018-0016.

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