

Changes in behavior and the stress-responsive system in the aging SHR and WKY rats after prolonged individual housing

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Motivation and Aim: Social isolation or loneliness in elderly is a serious problem in many developed and developing countries in the world including Russian Federation. Social isolation has objective and subjective dimensions that significantly influences its consequences for each individual. Prolonged social isolation is believed to negatively impact mental health, inducing psychiatric impairments and disturbances of cognitive functions. In older adults, the effects of isolation on mental health may significantly depend on age of a person and be strongly associated with individual perception of isolation. Furthermore, aging is associated with multimorbidity and cardiovascular and cerebrovascular diseases are among the most often reasons of morbidity and mortality in this group of people. The aim of the present study was to investigate the effects of prolonged social isolation on anxiety, depressive-like, and social behavior in the aging spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto (WKY). We also studied some biochemical indices of the stress-responsive system in these rats during and after the end of the isolation period.

Methods and Algorithms: Male 9–10-month-old SHR and WKY rats were used for the study. Animals were distributed into 4 groups according to their body weight and arterial pressure. The SHRi and WKYi rats were individually housed in opaque cages whereas the SHRs and WKYs rats remained in their home cages in groups of 2–3 animals. Individual housing continued for 12 weeks before the start of and then during the behavioral testing. Then, the animals were studied in the following battery of tests: sucrose preference test, open field test, elevated plus maze (EPM), three-chamber social test, and Barnes maze. The latter test was used to study learning ability and cognitive flexibility. The level of corticosterone was measured in the peripheral blood using ELISA. The expression of corticosterone-related genes was studied in the adrenals.

Results: Like in many other studies, increased locomotor and exploratory activity was revealed in SHR compared to WKY rats at the age of 13 months. The SHR rats performed increased number of open arm visits and time spent there as well as decreased stretching and higher risk-assessment behavior. However, we cannot suggest that the differences in behavior of animals in the EPM are determined by strain-specific trait/state anxiety only: rather they are associated with the hyperactivity of SHRs. This is supported by higher number of total entries into the maze arms. Surprisingly, social isolation induced only mild effect on anxiety in the open field test without influencing other affective-related behaviors. No effects of isolated housing on sociability or social

novelty preference were revealed. In contrast to emotional features, isolation induced some cognitive impairments observed during learning in the Barnes maze. WKYs, WKYi, and SHR rats were able to learn the spatial task in the maze whereas SHRi rats were bad learners. Moreover, WKYi, SHR and SHRi animals could not relearn the location of the safety box after its moving into the opposite position. Despite the adrenal gland hypertrophy in the SHRs, corticosterone levels remained stable within the period of isolation but the expression of nuclear glucocorticoid receptor (*Nr3c1*) mRNA in the adrenals was lower in the SHR as compared to WKY rats.

Conclusion: We can assume that in the aging SHR rats long-term social isolation significantly impaired cognitive abilities. Social isolation negatively influenced cognitive flexibility in both normotensive and hypertensive animals. Thus, hypertension significantly contributed to the effects of social isolation on cognitive functions but not on depressive-like behavior. Further, these impairments are not directly related to functions of the stress-responsive system.

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