

Roman high-avoidance rats as a putative schizophrenia-relevant model: Impairments in sensorimotor gating and working memory.

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The *Roman* high- and low-avoidance (RHA and RLA) rat lines/strains, have been bidirectionally selected and bred for their very good (RHA) or extremely poor (RLA) ability to acquire the two-way active avoidance task in a shuttle-box. They also differ in anxiety/fear (RLA > RHA) and stress susceptibility (RLA > RHA), in attention (RLA > RHA), cognitive (RLA > RHA) and impulsivity (RLA < RHA) traits, as well as in novelty-/drug-seeking (RLA < RHA) behavior and in (chronic) psychostimulant-induced locomotor and dopamine sensitization (RLA < RHA). In addition, inbred RHA-I rats show increased expression of 5-HT_{2A} receptors while they are devoid of mGluR2 expression in prefrontal cortex and hippocampus. As the 5-HT_{2A}/mGluR2 complex has been recently proposed as a possibly crucial mechanism in schizophrenia, the above-mentioned profiles suggest that RHA-I rats might be a model of some core attentional/cognitive and neurochemical features present in that disorder. Considering the need for valid rat models in the study of the schizophrenia, our objective was to systematically evaluate attentional (information processing, attentional filtering) and working memory (executive functions) differences between the Roman rat strains. We also included the NIH/Hs heterogeneous rat stock, that have not been previously evaluated in attentional functions, because it might be a useful tool as a control group, considering their genetic heterogeneity. To this aim, *Roman* male rats were evaluated in the PPI paradigm (prepulse inhibition) at postnatal days 30, 50 and 100 (PND30, 50 and 100), and in the Morris Water Maze (MWM) for "working memory" ("delayed matching-to-place task") at PND120. A group of male NIH-HS rats was also tested for PPI at PND100 and in the MWM at PND120 in parallel to RHA-I/RLA-I groups. Our results show no differences in PPI between male RHA-I and RLA-I rats at 30 (puberty) and 50 (adolescence) days of age, with significant differences –i.e. better PPI in RLA-I than in RHA-I rats- appearing when rats are 100 days old. This resembles the typical course of schizophrenia, which commonly shows its onset in the early adulthood. PPI levels from heterogeneous NIH-HS rats fell between RHA and RLA scores, although much closer to PPI responses shown by the RLA strain. In the working memory task (MWM), the RHA-I strain showed impaired working memory compared to RLA-I and NIH/HS groups, which again showed similar responses. In summary, RHA-I rats showed impairments in prepulse inhibition and in working memory. These results confirm our hypotheses, raising the

possibility that the RHA-I strain could be a valid animal model for the study of the schizophrenia.

Current and future studies from our group are aimed to complete the behavioral, psychopharmacological and neurochemical characterization of the RHA-I rat strain as a genetic animal model of schizophrenia.

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