

Rat strains with natural deficits in cognition for accelerating drug development.

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Rodent models can be useful for preclinical screening of compounds for patients with cognitive disorders like Alzheimer's, ADHD, autism and schizophrenia. Yet, the development of models for studying these complex neurological diseases often includes pharmacological and surgical manipulations, which can complicate the interpretation of a drug's efficacy. Here, we devised a streamlined version of the Morris Water Maze (MWM) protocol to assess the initial acquisition and strategy capabilities of inbred and consomic rats. We found that the Dahl salt-sensitive (SS) and Fawn Hooded Hypertensive (FHH) rats are naturally poor learners compared to normal Long Evans (LE) rats as they display only minimal decrease in latency (10-15%) to find the hidden platform during 3 days of acquisition training. Consomic rat strains have single chromosomes from the Brown Norway (BN) rat substituted onto the genetic background of the SS and the FHH. In contrast to the progenitor strains, the FHH.BN1 and SS.BN13 consomic animals exhibited a 30-40% decrease in latency to reach the hidden platform and learned the location at a rate comparable to the LE animals. Upon moving the platform to a novel location, the FHH.BN1 rats acquired the spatial rules necessary to adapt their strategy to a novel platform placement. However, the SS.BN13 animals displayed a perseverative behavior as they repeatedly visited the initial location of the platform. Systematic T-Maze studies confirmed the perseverative behavior of the SS.BN13 rats as they made 3-4 fold fewer correct choices to find the food reward in the reversal phase of the test compared to LE rats. The results suggest that the FHH, SS and SS.BN13 rats represent natural disease models with cognitive deficits similar to those found in patients with neurological diseases. The genetic rescue of the cognitive deficit in FHH rats (by substituting BN chromosome 1) demonstrates that consomic rats could be used for positional cloning of genes and pathways involved in learning and memory. Future studies include behavioral characterization of FHH.BN1 congenic rats and pharmacologic rescue of the cognition deficits in the FHH, SS and SS.BN13 rats using novel benzodiazepine compounds with subtype selectivity for subunits the GABA_A receptor.

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