

Enhanced learning and behavioral adaptation in the FHH.BN1 consomic rat



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Abstract

The use of chromosomal substitution rat strains, known as consomic rats, is an unexplored tool for examining the influence of genetics in behavioral paradigms. Consomic rats are created by introgressing single chromosomes from the Brown Norway (BN) rat on the genetic background of a Fawn-Hooded Hypertensive (FHH) rat resulting in a panel of 22 consomic strains (FHH.BN). The aim of the present research was to determine the influence that a BN chromosome 1 substitution has on the behavior of FHH rats. These FHH.BN1 consomic rats were compared with parent (FHH and BN) and Long Evans (LE) rats on several tasks including the Hot Plate Test for analgesia sensitivity, Open-Field Activity to assess anxiety and activity levels, and the Morris Water Maze to assess visuospatial abilities. For the Hot Plate Test, animals were placed in an enclosed chamber with a constant floor temperature of 50°C. The single trial was terminated when the rats displayed a "paw lick" movement. Results revealed that the latency to respond for the FHH rats was 2-fold higher than the BN rat. However, the FHH.BN1 consomic rats responded to the pain like the BN rats, which was significantly faster than the FHH. The Open-Field Activity test consisted of placing the animals into an open box with a 6x6 grid floor. The results of a single 5 minute trial indicate a trend for the FHH.BN1 rats to have a greater percentage of crossings on the inside grids than the FHH, BN and LE, which may indicate lower levels of anxiety. The MWM involved a five-day protocol with three days of acquisition followed by two days of testing in which the platform was moved to a novel location. Each day included four trials terminated when the rat reached the platform or when 1 minute had elapsed. The FHH.BN1 animals exhibited a significant increase in their ability to reach the hidden platform compared to the FHH rats. Together, these findings indicate that the substitution of BN chromosome 1 into the FHH genetic background results in behavioral phenotypes characterized by increased pain sensitivity, lower expression of anxiety, and enhanced learning in spatial navigation tasks. Future research will expand on the battery of behavioral tests in order to further characterize the traits identified in the FHH.BN1 consomic rat.

Introduction

Chromosomal substitution rat strains, known as consomic rats, were originally developed by researchers at the Medical College of Wisconsin as a rapid way to map quantitative trait loci throughout the genome and then to facilitate positional cloning of causal genes for complex human diseases such as cardiovascular disease, hypertension and end-stage renal disease. Consomic rats can be considered "natural" models used to study complex disease because all genes are intact (no gene knock-outs or knock-ins) and surgical and chemical induced lesions may not be required to elicit a desired phenotype. One panel of consomic rats was created by introgressing single chromosomes from the "normal" Brown Norway (BN) rat on the genetic background of the "disease" Fawn-Hooded Hypertensive (FHH) rat resulting in a panel of 22 consomic strains (FHH.BN). The FHH and BN rats are known to display a variety of other disease phenotypes, including depressive-like behavior, but to date are an unexplored tool for examining the influence of genetics in behavioral paradigms.

The current experiment sought to determine whether consomic rats can be a viable model for studying neurological disorders and be used to identify those pathways and genes responsible for the disorder. To do this, we characterized the baseline activity of the FHH and BN parental strains in a battery of six behavioral tests and then examined the influence of a BN chromosome 1 substitution on the behavior of FHH rats. The behavior and cognitive ability of the FHH.BN1 rat was also compared to the Long Evans (LE) rat as a way to gauge the behavioral response of a consomic rat to one of the standard models in the field. It was hypothesized that the FHH.BN1 consomic rat strain would exhibit a distinct behavioral phenotype unique from both of its parent strains (BN and FHH) while offering advantages compared to using the LE rat.

Methods

Subjects: Four strains of rats were used in the following experiment. For the Hot Plate Test of analgesia and Open-Field Activity experiments: 15 male LE (Harlan, Indianapolis, IN), 15 male BN (Charles River Laboratories), 10 male FHH, and 10 male FHH.BN1 (PhysioGenix colonies bred at Hilltop Lab Animals, Inc.). For the MWM: 25 male Long Evans hooded rats, 25 male BN, 10 male FHH, and 20 male FHH.BN1.

Procedure

All rodents were maintained on a 0.4% salt diet (Harlan-Teklad) and housed individually in standard shoebox cages. Food and water were available ad libitum.

Rats were first exposed to the Hot Plate Test for analgesia. Animals were placed in an enclosed chamber (Columbus Instruments) with a constant floor temperature of 50°C. Each animal received one trial, which was terminated when the rat exhibited a "paw lick" movement. Paw lick was defined as the rat lifting a paw off of the floor and moving it toward its mouth. The maximum time allowed for each test was 120 seconds.

Rats were then tested in the Open-Field. The open-field consisted of an open chamber (91.4 cm x 91.4 cm w x 57.8 cm h) with a 6x6 plexiglass grid placed in the bottom. Trials were videotaped from above the maze and the live feed was displayed on a 19 inch television in an adjoining room. Each animal received one five-minute trial that was videotaped and scored in a separate room. Exploration paths were traced on a scaled grid. Efforts were made to insure consistent lighting conditions across the open-field. Grid crossings were defined as four paws into a given grid. Rears were defined by an animal standing on hind quarters in the absence of grooming behavior.

Finally, visuospatial learning was assessed in the MWM. Rats were given four trials a day, one from each cardinal direction (N, S, E, W). Each trial lasted until the rat reached the hidden platform or for 60 seconds. There were approximately five minutes between trials. During the acquisition phase of training (first 3 days), the platform was placed in the NE quadrant (defined as the target quadrant). Following three days of acquisition, the platform was moved to the SW quadrant (the new target quadrant). Animals were tested for two days with the platform in the novel location. Swim path and search strategy were recorded by tracing swim path on a scaled grid.

All testing was assessed using the Statistical Package for the Social Sciences (SPSS) version 13 software and PRIZM software. Corrected error terms were used when appropriate.

Dependent Measures and Hypotheses

Hot Plate Test for analgesia

- Latency to paw lick
- Provides information related to pain sensitivity of animals
- Expected to be significantly different between parent strains and consomic strain

Open Field

- Total number of grids crossed, number of perimeter grids crossed, number of inside grids crossed, time spent in center grids, Boli, rears
- Measure of overall activity levels as well as anxiety
- Anticipated significant differences between parent strains and consomic strain

Morris Water Maze

- Success to reach platform, latency to reach platform, total quadrants entered, target quadrant entries
- Measure of visuospatial learning and memory
- Anticipated significant differences between parent strains and consomic strain

Conclusions, Implications, and Future Directions

- In several cases, FHH.BN1 rodents exhibit a distinct phenotype compared to the FHH rat indicating that gene(s) on chromosome 1 may be influencing the behavior.
- This behavioral phenotype can be characterized by increased pain sensitivity, decreased anxiety, and enhanced visuospatial learning.
- The use of chromosomal substitution rat strains, consomic rats, is an effective genetic tool in establishing unique, characterized phenotypes. If a significantly different phenotype is measured, the consomic strain can then be used in combination with the parental or other consomic rats for finding the causal genes influencing the behavior.
- Future studies will expand the battery of behavioral tests in order to further characterize the traits identified in the FHH.BN1 consomic rat. In addition, FHH.BN1 congenic strains and other consomic strains will be characterized for behavioral phenotypes.

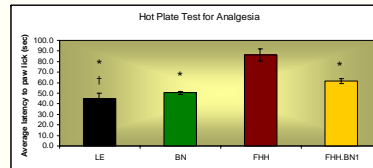


Figure 1. FHH.BN1 show increased pain sensitivity compared to FHH parent group. * indicates p<.05 from FHH, † indicates p<.05 from FHH.BN1.

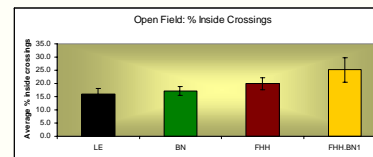


Figure 2. FHH.BN1 show a slightly higher percent of inside grid crossings, although no comparisons are significantly different. These results may indicate a potential decrease in anxiety levels in FHH.BN1 animals.

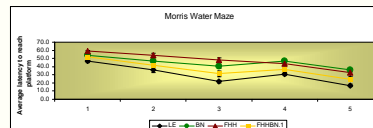


Figure 3. FHH.BN1 exhibit a significant decrease in the latency to find the platform in comparison with FHH and BN parent groups during acquisition. These results indicate enhanced visuospatial learning.

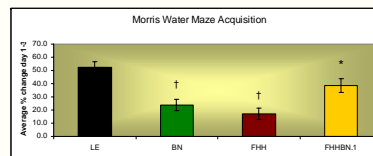


Figure 4. FHH.BN1 display stronger acquisition of the MWM via a greater % change from day 1 to 3 during training when compared with FHH and BN parent groups. * indicates p<.05 from FHH, † indicates p<.05 from LE.