The BacHD Rat: A New Rat Model of Huntington´s Disease Expressing the Full-Length Mutant *Huntingtin*

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ABSTRACT

The quality of behavioral studies on neurodegenerative diseases relies on the employment of adequate animal models. We recently developed a unique rat model of Huntington´s disease, which carries the full-length form of the causative gene *huntingtin*, inserted via a bacterial artificial chromosome (Bac). Advantages of the BacHD rat model are the replication of the protein context of the human disease due to the expression of the protein in its native form, combined with species-related benefits of the rat as an animal model. To characterize the BacHD rat, we implement classical behavioral tests as well as an automated home-cage system. First behavioral studies in BacHD rats demonstrate an early phenotype that resembles the human pathology. Thus the BacHD rat represents an appropriate new model to carry out basic research as well as therapeutic studies for Huntington´s Disease.

Author Keywords

Huntington's disease, full-length huntingtin, rat model, behavioral screening, PhenoMaster.

Ethical Statement

All of our animal experiments have been approved by an ethical committee and have been carried out in accordance with the German Animal Welfare Act (Deutsches Tierschutzgesetz).

INTRODUCTION

Huntington´s Disease (HD) is a fatal hereditary neurodegenerative disorder caused by an expanded CAG-repeat in the first Exon of the gene coding for the protein huntingtin. The patients suffer from chorea, psychiatric and metabolic disturbances as well as cognitive decline, leading to their death 10-15 years symptoms onset. Up to the present, there is no specific therapeutic for the disease available and the molecular pathogenesis still needs to be deciphered. For this reason, it is fundamental to have an animal model which replicates properly the human condition and therefore allows for more relevant results in basic research as well as in therapeutic studies.

THE BACHD RAT

We have developed a rat model of Huntington´s Disease by inserting the full-length mutant huntingtin into Sprague Dawley rats´ genome using the bacterial artificial chromosome (Bac) as a carrier. This BacHD rat model expresses human full-length huntingtin under the control of the human huntingtin promoter and its regulatory elements. Additional 20 kb upstream and 50 kb downstream sequences reduce the position effect of the transgene. The expansion in the huntingtin gene is a mixed CAA-CAG repeat, which produces a particular stability of the repeat length. Two LoxP sites, flanking the mutant huntingtin exon 1, allow for Cre-mediated excision.

The advantages of the BacHD rat model compared to other models of the disease are twofold, based on the species-specific differences between the animal models and the genetic background. The larger size of rats relative to mice facilitates repetitive physiological measurements and surgical manipulations as well as structural and functional imaging. Furthermore, cognitive abilities and their behavioral correlates are much better comparable between humans and rats. Due to the presence of the full-length huntingtin in its native 3-D structure (and unlike the situation in the fragment models of HD), cleavage and degradation processes as well as interactions with other proteins, which are instrumental to the disease pathogenesis in humans, are replicated.

MEASURING BEHAVIOR IN THE BACHD RAT

In order to characterize the BacHD rat, we have assessed behavior, metabolism and motor function with classical behavioral test approaches as well the automated home-cage system PhenoMaster (TSE Systems, Bad Homburg, Germany). With the age of 1 month, the BacHD rats already display impaired motor function demonstrated by less grip strength and a shorter latency to fall from a rotating rod. With 3 months, BacHD rats have reduced locomotor activity and food and water intake, measured in the PhenoMaster. Six months old animals show decreased exploratory behavior as well as decreased anxiety concluded from less locomotor activity and a higher ratio of locomotor activity in the centre versus the periphery during the first 15 min of a PhenoMaster recording. 9 months old BacHD rats have lower oxygen consumption rates and a constantly low respiratory quotient of 0.7, calculated from carbondioxide production and oxygen consumption sampled in the PhenoMaster. Furthermore, the animals display a higher amount of activity during the light cycle and reduced activity during the dark phase pointing to an incipient disruption of the circadian rhythm.

CONCLUSION

The BacHD rat is in many ways advantageous to other animal models of HD. It displays an early behavioral, metabolic and motor phenotype that resembles many of the human pathologies. Thus, the BacHD rat represents an appropriate new model to carry out basic research as well as therapeutic studies for Huntington´s Disease.