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Rodent models of huntington's disease: An overview

Gallilio Fernadez*
Department of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy

SUMMARY

Huntington's Disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. It is caused by a genetic mutation that leads to an abnormal expansion of CAG repeats in the Huntingtin (HTT) gene, resulting in an expanded polyglutamine tract in the huntingtin protein. This mutation induces a cascade of cellular dysfunctions culminating in the death of specific neuronal populations, predominantly in the striatum and cortex. While human studies provide critical insights, animal models, particularly rodent models, have been invaluable for understanding the pathophysiology of HD and for developing therapeutic strategies.

Keywords: Disease; Huntingtin; Neuronal; Striatum; Cascade; Young; Pathophysiology

Address for correspondence:

Gallilio Fernadez
Department of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy
E-mail: galliliofernadez@gmail.com

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INTRODUCTION

Rodent models offer several advantages for studying HD. They have relatively short lifespans, allowing researchers to observe disease progression and therapeutic outcomes within a reasonable timeframe. Their brains, though simpler, share fundamental similarities with human brains, making them useful for studying neurodegenerative processes. Additionally, the ability to manipulate the rodent genome enables the creation of precise genetic models that replicate key aspects of human HD pathology. Rodent models of HD can be broadly categorized into genetic models, transgenic models, and chemically induced models. Each type has its unique features and contributes differently to our understanding of HD. Genetic rodent models involve the introduction of human HD mutations into the rodent genome, usually through knock-in or knock-out techniques. These models are particularly valuable for studying the genetic and molecular mechanisms underlying HD.

Knock-in models involve inserting a fragment of the human HTT gene containing the expanded CAG repeats into the rodent genome. These models closely mimic the genetic mutation seen in human HD patients. These mice carry 150 CAG repeats in the endogenous mouse Htt gene. They exhibit age-dependent motor deficits, progressive striatal atrophy, and formation of nuclear inclusions containing mutant huntingtin protein, mirroring the human disease [1].

LITERATURE REVIEW

Knock-out models involve the deletion of the endogenous rodent Htt gene. These models help in understanding the normal function of huntingtin protein and the consequences of its loss. Complete deletion of the Htt gene results in embryonic lethality, highlighting the essential role of huntingtin in development. Conditional knock-out models, where Htt is deleted in specific tissues or at specific developmental stages, provide insights into huntingtin's functions in adults and its role in specific cell types. Transgenic models involve the introduction of mutant human HTT transgenes into the rodent genome. These models can express full-length or truncated versions of the human HTT gene with expanded CAG repeats, allowing for the study of mutant huntingtin protein's effects [2].

One of the most widely used HD models; R6/2 mice express exon 1 of the human HTT gene with approximately 150 CAG repeats. They exhibit rapid and severe disease progression, with motor deficits, weight loss, and early death. These mice are valuable for studying early and aggressive forms of HD and for testing potential therapies. These mice carry a yeast artificial chromosome containing the entire human HTT gene with 128 CAG repeats. They show progressive motor and cognitive deficits, striatal atrophy, and inclusion formation. The YAC128 model is particularly useful for studying the full-length mutant huntingtin protein's effects and for long-term therapeutic studies.

DISCUSSION

These mice express a truncated version of the human HTT gene containing the first 171 amino acids with 82 CAG repeats. They develop motor deficits, weight loss, and inclusion bodies. This model is useful for studying the role of specific huntingtin fragments in HD pathogenesis. These transgenic rats express a truncated human HTT gene with 51 CAG repeats. They exhibit motor deficits, cognitive impairments, and striatal atrophy. The larger size of rats compared to mice allows for more detailed behavioural and neuroanatomical studies. Chemically induced models use neurotoxins to selectively destroy specific neuronal populations, mimicking the neurodegeneration seen in HD. These models do not replicate the genetic basis of HD but are useful for studying disease mechanisms and testing neuroprotective therapies. 3-NP is a mitochondrial toxin that selectively targets striatal neurons, leading to neurodegeneration and motor deficits similar to those observed in HD. This model is used to study the role of mitochondrial dysfunction in HD and to test potential neuroprotective agents. QA is an excitotoxin that induces excitotoxic damage in the striatum, replicating the excitotoxicity observed in HD. This model is useful for studying the involvement of excitotoxic mechanisms in HD and for evaluating anti-excitotoxic therapies.

Mutant huntingtin protein with expanded polyglutamine tracts tends to misfold and aggregate, forming intracellular inclusions. These aggregates are a hallmark of HD pathology and are observed in various rodent models, including R6/2 and YAC128 mice. Studies have shown that these aggregates disrupt normal cellular functions, including protein degradation pathways, transcription, and mitochondrial function. Mutant huntingtin interacts with various transcription factors, altering the expression of numerous genes. Rodent models, particularly full-length transgenic models like YAC128 mice, have revealed widespread transcriptional dysregulation in the brain, affecting genes involved in synaptic function, energy metabolism, and stress responses. These findings suggest that transcriptional dysregulation is a critical component of HD pathogenesis.

Mitochondrial abnormalities are prominent in HD and have been extensively studied in rodent models. Models such as the 3-NP-treated mice exhibit mitochondrial dysfunction, including impaired respiration, reduced ATP production, and increased oxidative stress. These findings support the hypothesis that mitochondrial dysfunction contributes to neuronal degeneration in HD. Synaptic dysfunction is an early event in HD pathogenesis. Rodent models, including R6/2 and YAC128 mice, exhibit synaptic deficits such as impaired synaptic plasticity, reduced synaptic vesicle release, and altered neurotransmitter receptor expression. These alterations precede neuronal loss and are thought to contribute to the cognitive and motor deficits observed in HD [3-5].

Rodent models have been instrumental in testing potential therapeutic strategies for HD. Gene silencing approaches aim to reduce the production of mutant huntingtin protein. Antisense Oligonucleotides (ASOs) and RNA Interference (RNAi) have shown promise in rodent models. For instance, ASOs targeting the HTT mRNA have been effective in reducing huntingtin levels and ameliorating disease phenotypes in R6/2 and YAC128 mice. These approaches are now being translated into clinical trials. HDAC inhibitors, which modulate transcription, have shown neuroprotective effects in R6/2 mice by reducing mutant huntingtin aggregation and improving motor function. Compounds targeting mitochondrial dysfunction, such as coenzyme Q10 and creatine, have been tested in rodent models with some success in ameliorating motor deficits and extending lifespan.Anti-inflammatory drugs, such as minocycline and NSAIDs, have demonstrated efficacy in reducing neuroinflammation and improving behavioral outcomes in HD rodent models. Cell replacement strategies aim to replace lost neurons with healthy ones. Transplantation of neural stem cells or progenitor cells into the striatum of rodent models, such as QA-lesioned rats, has shown potential in restoring motor function and reducing neurodegeneration. These studies provide a foundation for developing cell-based therapies for HD.

No single rodent model fully recapitulates all aspects of human HD. Genetic models may not accurately represent the complete spectrum of disease pathology, while transgenic models often exhibit more rapid and severe phenotypes than those observed in human patients. Chemically induced models do not replicate the genetic basis of HD. Combining different models and developing new ones that better mimic the human disease are essential for advancing HD research. Despite promising results in rodent models, translating these findings into effective human therapies has been challenging. Differences in physiology, disease progression, and drug metabolism between rodents and humans can complicate translation. Rigorous preclinical testing and the development of more predictive models are needed to improve the success rate of clinical trials [6].

CONCLUSION

Advances in gene editing technologies, such as CRISPR/Cas9, hold promise for developing more accurate rodent models and for potential gene therapies. Additionally, humanized rodent models, which express human genes in a rodent background, may provide more relevant insights into human HD pathology and therapeutic responses. Understanding HD requires a multifaceted approach, integrating genetic, molecular, cellular, and behavioral studies. Combining rodent models with other experimental systems, such as patient-derived Induced Pluripotent Stem Cells (iPSCs) and organoids can provide a more comprehensive understanding of HD and facilitate the development of effective therapies. Rodent models have been indispensable in advancing our understanding of Huntington's disease. They have provided critical insights into the genetic, molecular, and cellular mechanisms underlying HD and have been instrumental in testing potential therapeutic strategies. While challenges remain in translating these findings into human therapies, ongoing advancements in model development and emerging technologies hold promise for overcoming these obstacles. The continued use of rodent models, alongside other experimental systems, will be crucial in the quest to develop effective treatments and ultimately a cure for Huntington's disease.

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CONFLICT OF INTEREST

None.

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