Chronic Diseases Journal

DOI: 10.22122/cdj.v13i2.633 Published by Vesnu Publications

A short review on toxin-induced animal models of Huntington's disease

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Review Article

Abstract

BACKGROUND: Huntington's disease (HD) is a neurodegenerative heredity motor and cognitional disorder. Different animal models of HD have been provided to study the different aspects of the disease such as pathophysiology and treatment and also the cure. Scientists need to choose the appropriate model for their goals, but it is often difficult because of the constraints. The low prevalence of HD often makes human studies impossible. For this reason, the availability of different animal models will be very helpful.

METHODS: To write this article, we searched "Huntington's Disease", "Huntington's Disease with Animal Models", and "Toxin-Induced Models with Huntington's disease", and then "3-Nitropropionic Acid", "Malonic Acid", "Kainic Acid", "Quinolinic Acid", all in combination with Huntington's Disease Animal Model in medical databases (such as PubMed, Scopus, etc.); then, all papers were reviewed, some excluded, and summarized as text and tables.

RESULTS: Animal models of HD are divided into two general categories: toxin-induced models and genetic models. Although it is clear that the genetic models are more compatible with HD, it is important to study all others to find the best models according to your research goals. 3-nitropropionic acid (3-NPA), malonic acid (MA), kainic acid (KA), and quinolinic acid (QA) are toxins used in past studies to induce different aspects of HD.

CONCLUSION: 3-NPA model is the most frequent model used for this purpose and after that, QA has been used more, but the other two models are less commonly used today. There are several different doses and routes of administration to induce toxin-induced HD models in different animals and for different purposes, and this diversity is misleading. That is why we have tried to compile all these models for researchers.

KEYWORDS: Animal Models; Huntington's Disease; Transgenic Model; 3-Nitropropionic Acid; Quinolinic Acid

Date of submission: 08 June 2024, ***Date of acceptance:*** 05 Feb. 2025

Citation: Fotoohi A. **A short review on toxin-induced animal models of Huntington's disease.** Chron Dis J 2025; 13(2): 103-9.

Introduction

Huntington's disease (HD) is a rare hereditary neurodegenerative disorder that affects the central nervous system (CNS).[1,2] It typically presents in mid-life and features movement disorders, such as chorea, alongside cognitive decline, including depression and dementia.[3,4] The causative gene was identified in 1993 by MacDonald et al.,[2] involving an abnormal (CAG)n repeat.[5-7] Further research revealed the defective gene's location on the short arm of chromosome 4 and confirmed its autosomal dominant inheritance pattern.[8] The primary pathological mechanism in HD is gamma-aminobutyric acid (GABA)ergic atrophy in medium spiny striatal neurons and cortical neurons, although the reasons for the selective damage to the striatum and cortex by the Huntingtin (HTT) protein remain unclear.[1,3,4,7] Various animal models have been developed to study different aspects of HD, including its pathophysiology and potential treatments. Selecting the appropriate model poses challenges, particularly due to limitations in

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technology and the cost of genetic-based HD models, which are not accessible to all research institutions.[9-12] Consequently, this discussion will briefly cover several toxin-induced HD animal models.

Methods

To write this article, we searched PubMed, Scopus, EMBASE, Cochrane, UpToDate, Google Scholar, and ClinicalKey databases using three main keywords: "Huntington Disease", "Huntington's Disease Animal Models", and "Huntington's Disease Toxin-Induced Models", without time restrictions. After reviewing the articles, we examined the toxins used to induce HD in animal models within the same databases. The toxins included 3-nitropropionic acid (3-NPA), malonic acid (MA), kainic acid (KA), and quinolinic acid (QA), all associated with HD animal models. Our inclusion and exclusion criteria focused on objectivity, repeatability, clarity, citation count, and journal validation. Finally, we summarized and organized all reviewed papers into text and tables.

Results

Rat and Mice Models of HD

Animal models of HD can be categorized into toxin-induced and genetic models (Figure 1).[13-16] While genetic models are more representative of HD, it is essential to explore all types to identify the best models for specific research objectives. For each animal study, data on the type of animal, study purpose, toxin doses (duration and frequency), number of animals, follow-up period, and outcomes have been collected.

3-NPA is an exotoxin derived from fungi (Aspergillus flavus, Astragalus, Arthrinium) and plants (Indigofera hendecaphylla).[9-12,19-23] Chronic administration of 3-NPA causes locomotor disorders in animals due to mitochondrial dysfunction, oxidative stress, and inhibition of antioxidant enzymes.[11,12,23-28] This systemic administration mimics the manifestations of HD because of selective mitochondrial dysfunction in the striatum and associated oxidative stress.[29,30] 3-NPA also induces both hypoactive and hyperactive phases. Consequently, 3-NPA closely resembles HD in symptoms and pathophysiology, making it a valuable model for treatment research as well as for neurotransplant studies.[31-35] 3-NPA has been given in different doses, durations, and routes – including subcutaneous (SC), intraperitoneal (IP), and intrastriatal (IS) – in various studies because it can cross the blood-brain barrier (BBB) (Table 1).[13,14,17,18]

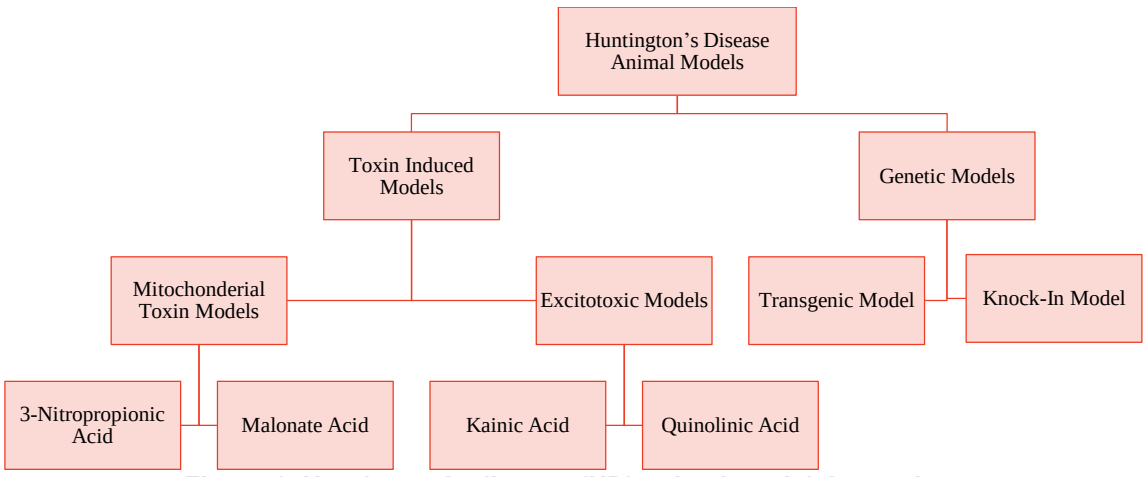

Figure 1. Huntington's disease (HD) animal models' overview

Table 1. 3-nitropropionic acid (3-NPA) doses for different mice and rats in different studies

S. No.	Dose	Animal
1	30 mg/kg/day for 1-2 days 10 mg/kg/day for 3-4 days, SC[18]	Male Sprague-Dawley rats
2	120 mg/kg/day for two days, IP[17]	Male Swiss Webster mice
3	140 mg/kg/day for 3-4 days, IP or SC[17]	C57BL/6
4	10 mg/kg for 5 days, IP[23]	Male Wistar rats
5	7.5 mg/kg BD for first 2 days, 3.75 mg/kg BD for 7 days, then 5 mg/kg BD for 9 days, IP 7.5 mg/kg twice daily for 10 days, IP[19]	Male Sprague-Dawley rats
6	20 mg/kg/day for 2 or 3 days, SC then 20 mg/kg/day, for 4 days, IP[20]	Male Wistar rats
7	10 mg/kg/day, once every four days for 28 days, IP[26]	Male Sprague-Dawley rats
8	20 mg/kg/day for 3-4 days, IP[14]	Sprague-Dawley rats
9	10 mg/kg/day for 14 days, IP[24]	Male Wistar rats
10	750 nmol bilateral IS[21]	Male Sprague-Dawley rats
11	60 mg/kg BD for 5 days[22]	Male CD1 mice
12	63 mg/kg/day for 5 days, SC[32]	Male Lewis rats
13	60 mg/kg BD for 1 day, then 80 mg/kg BD for 1 day on second day, IP[25]	Male C57BL/6 mice
14	125 mg/kg/day for 2-3 days, IP[34]	BALB/c
15	100 mg/kg/day for 2 days, IP[35]	129SvEMS, FVB/n
16	10 mg/kg/day for 2-3 days, IP[33]	Fischer rats

BD: Twice a day; IP: Intraperitoneal; SC: Subcutaneous; IS: Intrastriatal

MA Model

Although MA can stop the adenosine triphosphate (ATP) production cycle in the neurons mitochondria, but there is an important difference; MA cannot cross BBB and for this reason, it cannot be administrated IP or IS.[36] MA produces striatal lesions by indirect N-methyl-D-aspartate (NMDA) receptor activation,[37] and inhibition of succinate dehydrogenase (SDH),[38,39] and also apoptosis. But there are still doubts about the main mechanism of MA neurotoxicity.[6] To administrate MA, it is necessary to anesthetize the animal and then administer IS injection. Various doses are mentioned for MA in different studies that are shown in table 2.[40-43] After that, table 2 shows the mean and standard deviation (SD) of pain intensity. The results of this analysis regarding the F value on pain intensity have been shown in table 3.

KA Model

The KA model of HD is an excitotoxic model that leads to excessive activation of NMDA receptors, resulting in reduced GABA activity and increased acetylcholine, glutamate, and dopamine levels.[44-46] Consequently, KA administration serves as a relevant model for HD.[47,48] Behaviorally, KA induces impaired learning and memory following striatal lesions, making it a suitable model for studying HD.[49-51] Similar to other models, the KA approach selectively causes apoptosis in the striatum, with administration occurring only in that region. While various doses have been used in past studies to induce HD symptoms, this model has fallen out of favor in the last decade due to its tendency to damage nerve fibers at higher concentrations and create remote lesions.[44,47,52]

Table 2. Malonic acid (MA) doses for different mice and rats in different studies

S. No.	Dose	Animal
1	Methoxyflurane and malonate (1.4 µmol in 0.7 µmol, IS to left striatum)[36]	Mice
2	1 or 2 µmol, IS injection[38]	Male Sprague-Dawley rats
3	1.33 M/1 µl, IS injection to left striatum[39]	Male Sprague-Dawley rats
4	6 µmol/4 µl, IS injection to right striatum[41]	Male Wistar rats
5	2 M/1 µl, IS injection to left striatum[39,40]	Male Sprague-Dawley rats

IS: Intrastriatal

Table 3. Quinolinic acid (QA) doses for different mice and rats in different studies

S. No.	Dose	Animal
1	210 nmol/0.7 µl, IS injection[53]	Male Wistar rats
2	120 nmol/µl per side, bilateral IS injection[54]	Male Wistar rats
3	300 nmol/4 µl, unilateral IS injection in right striatum[55]	Male Wistar rats
4	200 nmol/2 µl, bilateral IS injection[56]	Male Sprague-Dawley rats

IS: Intrastriatal

QA Model

The QA model of HD was developed after the KA model. QA, an intermediate in tryptophan metabolism, can cross the BBB and elevate neurotoxic levels that mimic HD symptoms.[53] This model leads to NMDA receptor overactivation, resulting in GABA hypoactivation and the hyperactivation of acetylcholine, glutamate, and dopamine, similar to the KA model.[54] Since QA cannot cross the BBB, it must be administered IS.[55,56] There is no definitive dosage for QA; various doses have been used, as shown in table 3.

Discussion

HD is a hereditary neurodegenerative disorder characterized by involuntary choreiform movements, cognitive deficits, and psychological disturbances. It affects thousands globally and imposes significant costs on healthcare systems. While various drugs can help manage symptoms, only tetrabenazine has been Food and Drug Administration (FDA)-approved for controlling movement disorders associated with HD. There is currently no definitive cure, but gene silencing projects are underway. Research on the pathophysiology, pharmacology, and new treatment approaches for HD is essential. Animal models are often used for initial studies; however, many of these models can be expensive and time-consuming and require advanced technology, which may not be accessible to all research centers. This is why some studies still utilize simpler, low-cost, traditional models of HD. It is important to recognize that there are no inherently good or bad models, but rather models that are proportionate or disproportionate to the specific research objectives.

Conclusion

Toxin-induced animal models have proven valuable tools for studying HD, offering unique insights into the disease pathophysiology and providing platforms for potential therapeutic interventions. Among the toxin-induced models, 3-NPA remains the most widely-used due to its ability to closely mimic symptoms and underlying mechanisms of HD, particularly in the striatum. QA follows closely in usage, while MA and KA are less frequently employed today, due to their limitations in reproducing the full spectrum of HD features or their invasive administration requirements. Despite these differences, each toxin-induced model has its own merits depending on the specific goals of a study, whether focused on mitochondrial dysfunction, excitotoxicity, or neurodegeneration. The variability in dosing and administration routes among studies highlights the need for standardized protocols to minimize discrepancies and improve reproducibility. Moving forward, continued exploration of these models, alongside emerging genetic models, will be essential for refining our understanding of HD and developing more effective treatments. Researchers must consider the strengths and limitations of each model to ensure they are selecting the most appropriate model for their investigative studies.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

I would like to express my special thanks to my supervisors, Professor Esmail Izadpanah and Mohammad Raman Moloodi.

Financials support and sponsorship

None.

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