



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

Ahmad Fotoohi¹

Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran

Review Article

Abstract

BACKGROUND: Huntington's disease (HD) is a neurodegenerative hereditary motor and cognitive 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

Corresponding Author:

Ahmad Fotoohi; Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran
Email: ahmadfotoohi@gmail.com

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}

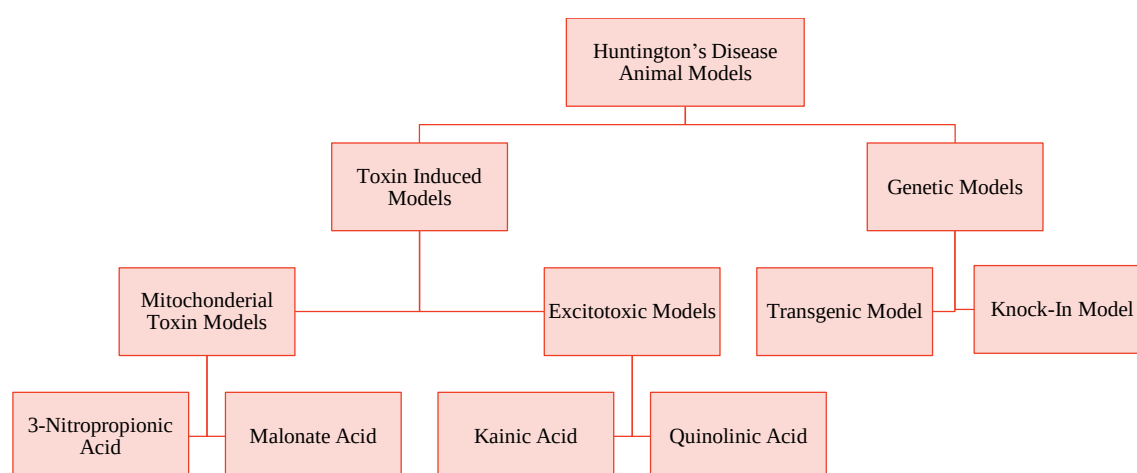


Figure 1. Huntington's disease (HD) animal models' overview

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	Male Sprague-Dawley rats
2	10 mg/kg/day for 3-4 days, SC ¹⁸	
3	120 mg/kg/day for two days, IP ¹⁷	Male Swiss Webster mice
4	140 mg/kg/day for 3-4 days, IP or SC ¹⁷	C57BL/6
5	10 mg/kg for 5 days, IP ²³	Male Wistar rats
6	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	Male Sprague-Dawley rats
7	7.5 mg/kg twice daily for 10 days, IP ¹⁹	
8	20 mg/kg/day for 2 or 3 days, SC then 20 mg/kg/day, for 4 days, IP ²⁰	Male Wistar rats
9	10 mg/kg/day, once every four days for 28 days, IP ²⁶	Male Sprague-Dawley rats
10	20 mg/kg/day for 3-4 days, IP ¹⁴	Sprague-Dawley rats
11	10 mg/kg/day for 14 days, IP ²⁴	Male Wistar rats
12	750 nmol bilateral IS ²¹	Male Sprague-Dawley rats
13	60 mg/kg BD for 5 days ²²	Male CD1 mice
14	63 mg/kg/day for 5 days, SC ³²	Male Lewis rats
15	60 mg/kg BD for 1 day, then 80 mg/kg BD for 1 day on second day, IP ²⁵	Male C57BL/6 mice
16	125 mg/kg/day for 2-3 days, IP ³⁴	BALB/c
17	100 mg/kg/day for 2 days, IP ³⁵	129SvEMS, FVB/n
18	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 μ mol in 0.7 μ mol, IS to left striatum) ³⁶	Mice
2	1 or 2 μ mol, IS injection ³⁸	Male Sprague-Dawley rats
3	1.33 M/1 μ l, IS injection to left striatum ³⁹	Male Sprague-Dawley rats
4	6 μ mol/4 μ l, IS injection to right striatum ⁴¹	Male Wistar rats
5	2 M/1 μ l, 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: Intrastratial

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.

References

1. Roos RA. Huntington's disease: A clinical review. *Orphanet J Rare Dis*. 2010; 5: 40.
2. MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993; 72(6): 971-83.
3. Nakamura S. Huntington's disease-advances in gene mapping. *Nihon Rinsho*. 1993; 51(9): 2481-7. [In Japanese].
4. Bates G, Tabrizi S, Jones L, editors. *Huntington's Disease*. 4th ed. New York: Oxford University Press; 2014.
5. Hayden MR. *Huntington's chorea*. London, UK: Springer London; 1981.
6. Kaur N, Jamwal S, Gill HK, Bansal PK. Animal models of Huntington's disease. In: Bansal PK, Deshmukh R, editors. *Animal models of neurological disorders: Principle and working procedure for animal models of neurological disorders*. Singapore: Springer Singapore; 2017. p. 43-57.
7. Brouillet E, Condé F, Beal MF, Hantraye P. Replicating Huntington's disease phenotype in experimental animals. *Prog Neurobiol*. 1999; 59(5): 427-68.
8. Menalled L, Brunner D. Animal models of Huntington's disease for translation to the clinic: Best practices. *Mov Disord*. 2014; 29(11): 1375-90.
9. Pouladi MA, Morton AJ, Hayden MR. Choosing an animal model for the study of Huntington's disease. *Nat Rev Neurosci*. 2013; 14(10): 708-21.
10. Ramaswamy S, McBride JL, Kordower JH. Animal models of Huntington's disease. *Ilar j*. 2007; 48(4): 356-73.
11. Wei D-L, Chang S-C, Lin S-C, Doong M-L, Jong S-C. Production of 3-nitropropionic acid by arthrionium species. *Curr Microbiol*. 1994; 28(1): 1-5.
12. Borlongan CV, Koutouzis TK, Sanberg PR. 3-Nitropropionic acid animal model and Huntington's disease. *Neurosci Biobehav Rev*. 1997; 21(3): 289-93.
13. Pelegrí C, Duran-Vilaregut J, del Valle J, Crespo-Biel N, Ferrer I, Pallàs M, et al. Cell cycle activation in striatal neurons from Huntington's disease patients and rats treated with 3-nitropropionic acid. *Int J Dev Neurosci*. 2008; 26(7): 665-71.
14. Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, et al. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. *J Neurosci*. 1993; 13(10): 4181-92.
15. Brouillet E, Jacquard C, Bizat N, Blum D. 3-Nitropropionic acid: A mitochondrial toxin to uncover physiopathological mechanisms underlying striatal degeneration in Huntington's disease. *J Neurochem*. 2005; 95(6): 1521-40.
16. Stavrovskaya A, Yamshchikova N, Ol'shanskiy A, Konovalova E, Illarionovskiy S. Transplantation of neuronal precursors derived from induced pluripotent stem cells into the striatum of rats with the toxin-induced model of Huntington's disease. *Hum Physiol*. 2017; 43(8): 881-5.
17. Gould DH, Gustine DL. Basal ganglia degeneration, myelin alterations, and enzyme inhibition induced in mice by the plant toxin 3-nitropropanoic acid. *Neuropathol Appl Neurobiol*. 1982; 8(5): 377-93.
18. Hamilton BF, Gould DH. Nature and distribution of brain lesions in rats intoxicated with 3-nitropropionic acid: A type of hypoxic (energy deficient) brain damage. *Acta Neuropathol*. 1987; 72(3): 286-97.
19. Guyot MC, Hantraye P, Dolan R, Palfi S, Mazière M, Brouillet E. Quantifiable bradykinesia, gait abnormalities and Huntington's disease-like striatal lesions in rats chronically treated with 3-nitropropionic acid. *Neuroscience*. 1997; 79(1): 45-56.
20. Nishino H, Kumazaki M, Fukuda A, Fujimoto I, Shimano Y, Hida H, et al. Acute 3-nitropropionic acid intoxication induces striatal astrocytic cell death and dysfunction of the blood-brain barrier: Involvement of dopamine toxicity. *Neurosci Res*. 1997; 27(4): 343-55.
21. Shear DA, Dong J, Gundy CD, Haik-Creguer KL, Dunbar GL. Comparison of intra-striatal injections of quinolinic acid and 3-nitropropionic acid for use in animal models of Huntington's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 1998; 22(7): 1217-40.
22. Kim GW, Copin JC, Kawase M, Chen SF, Sato S, Gobbel GT, et al. Excitotoxicity is required for induction of oxidative stress and apoptosis in mouse striatum by the mitochondrial toxin, 3-nitropropionic acid. *J Cereb Blood Flow Metab*. 2000; 20(1): 119-29.
23. Szabó A, Papp A, Nagymajtényi L. Effects of 3-nitropropionic acid in rats: General toxicity and functional neurotoxicity. *Arh Hig Rada Toksikol*.

- 2005; 56(4): 297-302.
24. Kumar P, Kumar A. Effect of lycopene and epigallocatechin-3-gallate against 3-nitropropionic acid induced cognitive dysfunction and glutathione depletion in rat: A novel nitric oxide mechanism. *Food Chem Toxicol.* 2009; 47(10): 2522-30.
 25. Jang M, Lee MJ, Cho IH. Ethyl pyruvate ameliorates 3-nitropropionic acid-induced striatal toxicity through anti-neuronal cell death and anti-inflammatory mechanisms. *Brain Behav Immun.* 2014; 38: 151-65.
 26. Borlongan CV, Koutouzis TK, Randall TS, Freeman TB, Cahill DW, Sanberg PR. Systemic 3-nitropropionic acid: behavioral deficits and striatal damage in adult rats. *Brain Res Bull.* 1995; 36(6): 549-56.
 27. Domenici MR, Chiodi V, Averna M, Armida M, Pèzzola A, Peponi R, et al. Neuronal adenosine A(2A) receptor overexpression is neuroprotective towards 3-nitropropionic acid-induced striatal toxicity: a rat model of Huntington's disease. *Purinergic Signal.* 2018; 14(3): 235-43.
 28. Sidhu A, Diwan V, Kaur H, Bhateja D, Singh CK, Sharma S, et al. Nicotinamide reverses behavioral impairments and provides neuroprotection in 3-nitropropionic acid induced animal model of Huntington's disease: implication of oxidative stress- poly(ADP- ribose) polymerase pathway. *Metab Brain Dis.* 2018; 33(6): 1911-21.
 29. Ramachandran S, Thangarajan S. Thymoquinone loaded solid lipid nanoparticles counteracts 3-Nitropropionic acid induced motor impairments and neuroinflammation in rat model of Huntington's disease. *Metab Brain Dis.* 2018; 33(5): 1459-70.
 30. Orozco-Ibarra M, García-Morales J, Calvo-Silva FJ, Fernández-Valverde F, Serrano-García N. Striatal mitochondria response to 3-nitropropionic acid and fish oil treatment. *Nutr Neurosci.* 2018; 21(2): 132-42.
 31. Calderón Guzmán D, Osnaya Brizuela N, Ortiz Herrera M, Juárez Olguín H, Valenzuela Peraza A, Hernández García E, et al. Folic acid increases levels of GHS in brain of rats with oxidative stress induced with 3-nitropropionic acid. *Arch Physiol Biochem.* 2020; 126(1): 1-6.
 32. Park JE, Lee ST, Im WS, Chu K, Kim M. Galantamine reduces striatal degeneration in 3-nitropropionic acid model of Huntington's disease. *Neurosci Lett.* 2008; 448(1): 143-7.
 33. Ouay S, Bizat N, Altairac S, Ménétrat H, Mittoux V, Condé F, et al. Major strain differences in response to chronic systemic administration of the mitochondrial toxin 3-nitropropionic acid in rats: Implications for neuroprotection studies. *Neuroscience.* 2000; 97(3): 521-30.
 34. Alexi T, Hughes PE, Knüsel B, Tobin AJ. Metabolic compromise with systemic 3-nitropropionic acid produces striatal apoptosis in Sprague-Dawley rats but not in BALB/c ByJ mice. *Exp Neurol.* 1998; 153(1): 74-93.
 35. Gabrielson KL, Hogue BA, Bohr VA, Cardounel AJ, Nakajima W, Kofler J, et al. Mitochondrial toxin 3-nitropropionic acid induces cardiac and neurotoxicity differentially in mice. *Am J Pathol.* 2001; 159(4): 1507-20.
 36. Klivenyi P, Andreassen OA, Ferrante RJ, Dedeoglu A, Mueller G, Lancelot E, et al. Mice deficient in cellular glutathione peroxidase show increased vulnerability to malonate, 3-nitropropionic acid, and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *J Neurosci.* 2000; 20(1): 1-7.
 37. Henshaw R, Jenkins BG, Schulz JB, Ferrante RJ, Kowall NW, Rosen BR, et al. Malonate produces striatal lesions by indirect NMDA receptor activation. *Brain Res.* 1994; 647(1): 161-6.
 38. Greene JG, Porter RH, Eller RV, Greenamyre JT. Inhibition of succinate dehydrogenase by malonic acid produces an "excitotoxic" lesion in rat striatum. *J Neurochem.* 1993; 61(3): 1151-4.
 39. Sagredo O, González S, Aroyo I, Pazos MR, Benito C, Lastres-Becker I, et al. Cannabinoid CB2 receptor agonists protect the striatum against malonate toxicity: Relevance for Huntington's disease. *Glia.* 2009; 57(11): 1154-67.
 40. Valdeolivas S, Pazos MR, Bisogno T, Piscitelli F, Iannotti FA, Allarà M, et al. The inhibition of 2-arachidonoyl-glycerol (2-AG) biosynthesis, rather than enhancing striatal damage, protects striatal neurons from malonate-induced death: A potential role of cyclooxygenase-2-dependent metabolism of 2-AG. *Cell Death Dis.* 2013; 4(10): e862.
 41. Kalonia H, Kumar P, Kumar A, Nehru B. Protective effect of montelukast against quinolinic acid/malonic acid induced neurotoxicity: Possible behavioral, biochemical, mitochondrial and tumor necrosis factor- α level alterations in rats. *Neuroscience.* 2010; 171(1): 284-99.
 42. Kumar A, Sharma N, Mishra J, Kalonia H. Synergistical neuroprotection of rofecoxib and statins against malonic acid induced Huntington's disease like symptoms and related cognitive dysfunction in rats. *Eur J Pharmacol.* 2013; 709(1-3): 1-12.
 43. Toulmond S, Tang K, Bureau Y, Ashdown H, Degen S, O'Donnell R, et al. Neuroprotective effects of M826, a reversible caspase-3 inhibitor, in the rat malonate model of Huntington's disease. *Br J Pharmacol.* 2004; 141(4): 689-97.
 44. Schwarcz R, Coyle JT. Striatal lesions with kainic acid: Neurochemical characteristics. *Brain Res.* 1977;

- 127(2): 235-49.
45. Coyle JT, Schwarcz R. Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. *Nature*. 1976; 263(5574): 244-6.
 46. Sanberg PR, Lehmann J, Fibiger HC. Impaired learning and memory after kainic acid lesions of the striatum: A behavioral model of Huntington's disease. *Brain Res*. 1978; 149(2): 546-51.
 47. Deckel AW, Robinson RG, Coyle JT, Sanberg PR. Reversal of long-term locomotor abnormalities in the kainic acid model of Huntington's disease by day 18 fetal striatal implants. *Eur J Pharmacol*. 1983; 93(3-4): 287-8.
 48. Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, et al. Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. *Neuron*. 2002; 33(6): 849-60.
 49. Arregui A, Emson PC, Spokes EG. Angiotensin-converting enzyme in substantia nigra: Reduction of activity in Huntington's disease and after intrastriatal kainic acid in rats. *Eur J Pharmacol*. 1978; 52(1): 121-4.
 50. Stoy N, Mackay GM, Forrest CM, Christofides J, Egerton M, Stone TW, et al. Tryptophan metabolism and oxidative stress in patients with Huntington's disease. *J Neurochem*. 2005; 93(3): 611-23.
 51. Schwarcz R, Guidetti P, Sathyaikumar KV, Muchowski PJ. Of mice, rats and men: Revisiting the quinolinic acid hypothesis of Huntington's disease. *Prog Neurobiol*. 2010; 90(2): 230-45.
 52. Smith AJ, Stone TW, Smith RA. Neurotoxicity of tryptophan metabolites. *Biochem Soc Trans*. 2007; 35(Pt 5): 1287-9.
 53. Pintor A, Tebano MT, Martire A, Grieco R, Galluzzo M, Scattoni ML, et al. The cannabinoid receptor agonist WIN 55,212-2 attenuates the effects induced by quinolinic acid in the rat striatum. *Neuropharmacology*. 2006; 51(5): 1004-12.
 54. Pérez-De La Cruz V, Elinos-Calderón D, Robledo-Arratia Y, Medina-Campos ON, Pedraza-Chaverrí J, Ali SF, et al. Targeting oxidative/nitrergic stress ameliorates motor impairment, and attenuates synaptic mitochondrial dysfunction and lipid peroxidation in two models of Huntington's disease. *Behav Brain Res*. 2009; 199(2): 210-7.
 55. Kalonia H, Kumar P, Kumar A. Attenuation of proinflammatory cytokines and apoptotic process by verapamil and diltiazem against quinolinic acid induced Huntington like alterations in rats. *Brain Res*. 2011; 1372: 115-26.
 56. Mishra J, Kumar A. Improvement of mitochondrial NAD(+)/FAD(+)-linked state-3 respiration by caffeine attenuates quinolinic acid induced motor impairment in rats: Implications in Huntington's disease. *Pharmacol Rep*. 2014; 66(6): 1148-55.