

# CHAPTER 1

## THE INVOLVEMENT OF XANTHINE OXIDASE AND URIC ACID IN NEUROLOGICAL DISORDERS

Nurcan DEDEOĞLU<sup>1</sup>

### GİRİŞ

Oxidative stress has a critical role in the pathophysiology of neurological disorders. The excessive generation of reactive oxygen species (ROS) and free radicals harms neuronal cells, inducing lipid, protein, and DNA damage that subsequently leads to cell death. Xanthine oxidoreductase (XOR), commonly recognized as Xanthine oxidase (XO, EC 1.17.3.2), the terminal enzyme in purine catabolism, has a critical role in this process. XO facilitates the transformation of hypoxanthine into xanthine and xanthine into uric acid through the transfer of electrons to oxygen. ROS species, superoxide anion ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ), were generated by this process[1].

XO-induced oxidative stress in high oxygen-consuming tissues, such as the brain, significantly contributes to the onset of several neurological disorders, including Parkinson's, Alzheimer's, Multiple Sclerosis, and ischemic stroke [2]. Consequently, XO has attracted considerable interest for its potential as a therapeutic target and biomarker.

This chapter discusses the relationship between xanthine oxidoreductase (XOR), commonly known as xanthine oxidase (XO), a crucial enzyme of purine catabolism and also a significant producer of reactive oxygen species (ROS), and its connection to neurological disorders.

### OXIDATIVE STRESS AND XANTHINE OXIDASE

Numerous neurological disorders, notably Parkinson's disease, Alzheimer's dementia, schizophrenia, amyotrophic lateral sclerosis, and, more recently, depres-

<sup>1</sup> Asst. Prof. Dr., Adana Alparslan Türkeş Science and Technology University, ndedeoglu@atu.edu.tr, ORCID iD 0000-0002-4008-2587

diseases. The clinical implementation of XOR inhibitors and the integration of antioxidant-based therapeutic strategies further emphasize the translational significance of the enzyme. However, given the divergence of current findings and the multifactorial nature of neurodegenerative disorders, large-scale, prospective, and randomized clinical trials are warranted to establish the long-term safety and therapeutic efficacy of XOR-targeted therapies.

## REFERENCES

1. M. G. Battelli, M. Bortolotti, L. Polito, and A. Bolognesi, "The role of xanthine oxidoreductase and uric acid in metabolic syndrome," *Biochim Biophys Acta Mol Basis Dis*, vol. 1864, no. 8, pp. 2557–2565, 2018, doi: 10.1016/j.bbadis.2018.05.003.
2. C. E. Berry and J. M. Hare, "Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications," *J Physiol*, pp. 589–606, 2004, doi: DOI:10.1113/jphysiol.2003.055913.
3. T. M. Michel *et al.*, "Increased xanthine oxidase in the thalamus and putamen in depression," *World Journal of Biological Psychiatry*, vol. 11, no. 2 PART 2, pp. 314–320, 2010, doi: 10.3109/15622970802123695.
4. A. Veljković *et al.*, "Xanthine Oxidase/Dehydrogenase Activity as a Source of Oxidative Stress in Prostate Cancer Tissue," *Diagnostics*, vol. 10, no. 9, p. 668, Sep. 2020, doi: 10.3390/diagnostics10090668.
5. R. Harrison, "Structure And Function Of Xanthine Oxidoreductase: Where Are We Now?," 2002.
6. K. Ichida, Y. Amaya, K. Okamoto, and T. Nishino, "Mutations associated with functional disorder of xanthine oxidoreductase and hereditary xanthinuria in humans," 2012, MDPI AG. doi: 10.3390/ijms131115475.
7. M. Yamaguchi *et al.*, "The effects of xanthine oxidoreductase inhibitors on oxidative stress markers following global brain ischemia reperfusion injury in C57BL/6 mice," *PLoS One*, vol. 10, no. 7, Jul. 2015, doi: 10.1371/journal.pone.0133980.
8. R. J. Johnson, M. A. Lanaspá, and E. A. Gaucher, "Uric Acid: A Danger Signal From the RNA World That May Have a Role in the Epidemic of Obesity, Metabolic Syndrome, and Cardiorenal Disease: Evolutionary Considerations," *Semin Nephrol*, vol. 31, no. 5, pp. 394–399, Sep. 2011, doi: 10.1016/j.semnephrol.2011.08.002.
9. H. Sekizuka, "Uric acid, xanthine oxidase, and vascular damage: potential of xanthine oxidoreductase inhibitors to prevent cardiovascular diseases," 2022. doi: 10.1038/s41440-022-00891-7.
10. T. Settle, "The Role of Uric Acid as an Antioxidant in Selected Neurodegenerative Disease Pathogenesis: A Short Review," *Brain Disord Ther*, vol. 03, no. 03, pp. 239–247, 2014, doi: 10.4172/2168-975x.1000129.
11. P. Higgins, J. Dawson, and M. Walters, "The Potential for Xanthine Oxidase Inhibition in the Prevention and Treatment of Cardiovascular and Cerebrovascular Disease," *Cardiovasc Psychiatry Neurol*, vol. 2009, pp. 1–9, Nov. 2009, doi: 10.1155/2009/282059.
12. M. G. Scioli *et al.*, "Oxidative Stress and New Pathogenetic Mechanisms in Endothelial Dysfunction: Potential Diagnostic Biomarkers and Therapeutic Targets," *J Clin Med*, vol. 9, no. 6, p. 1995, Jun. 2020, doi: 10.3390/jcm9061995.
13. F. Wang *et al.*, "Fundamental Mechanisms of the Cell Death Caused by Nitrosative Stress," *Front Cell Dev Biol*, vol. 9, Sep. 2021, doi: 10.3389/fcell.2021.742483.
14. M. Bortolotti, L. Polito, M. G. Battelli, and A. Bolognesi, "Xanthine oxidoreductase: One enzyme for multiple physiological tasks," May 01, 2021, *Elsevier B.V.* doi: 10.1016/j.redox.2021.101882.
15. M. G. Battelli, A. Bolognesi, and L. Polito, "Pathophysiology of circulating xanthine oxidoreductase: New emerging roles for a multi-tasking enzyme," *Biochimica et Biophysica Acta (BBA)*

- *Molecular Basis of Disease*, vol. 1842, no. 9, pp. 1502–1517, Sep. 2014, doi: 10.1016/j.bba-dis.2014.05.022.
16. C. O. Reichert *et al.*, “Ferroptosis Mechanisms Involved in Neurodegenerative Diseases,” *Int J Mol Sci*, vol. 21, no. 22, p. 8765, Nov. 2020, doi: 10.3390/ijms21228765.
  17. M. G. Battelli, M. Bortolotti, A. Bolognesi, and L. Polito, “Pro-Aging Effects of Xanthine Oxidoreductase Products,” *Antioxidants*, vol. 9, no. 9, p. 839, Sep. 2020, doi: 10.3390/antiox9090839.
  18. G. F. Crotty, A. Ascherio, and M. A. Schwarzschild, “Targeting urate to reduce oxidative stress in Parkinson disease,” *Exp Neurol*, vol. 298, pp. 210–224, Dec. 2017, doi: 10.1016/j.exp-neurol.2017.06.017.
  19. V. Pegoretti, K. A. Swanson, J. R. Bethea, L. Probert, U. L. M. Eisel, and R. Fischer, “Inflammation and Oxidative Stress in Multiple Sclerosis: Consequences for Therapy Development,” *Oxid Med Cell Longev*, vol. 2020, pp. 1–19, May 2020, doi: 10.1155/2020/7191080.
  20. B. Dąbrowska-Bouta, L. Strużyńska, M. Sidoryk-Węgrzynowicz, and G. Sulkowski, “Memantine Modulates Oxidative Stress in the Rat Brain following Experimental Autoimmune Encephalomyelitis,” *Int J Mol Sci*, vol. 22, no. 21, p. 11330, Oct. 2021, doi: 10.3390/ijms222111330.
  21. M. Dimitrijević *et al.*, “Sex Difference in Oxidative Stress Parameters in Spinal Cord of Rats with Experimental Autoimmune Encephalomyelitis: Relation to Neurological Deficit,” *Neurochem Res*, vol. 42, no. 2, pp. 481–492, Feb. 2017, doi: 10.1007/s11064-016-2094-7.
  22. M. Moccia *et al.*, “Uric acid in relapsing–remitting multiple sclerosis: a 2-year longitudinal study,” *J Neurol*, vol. 262, no. 4, pp. 961–967, Apr. 2015, doi: 10.1007/s00415-015-7666-y.
  23. E. Tönnies and E. Trushina, “Oxidative Stress, Synaptic Dysfunction, and Alzheimer’s Disease,” *Journal of Alzheimer’s Disease*, vol. 57, no. 4, pp. 1105–1121, Apr. 2017, doi: 10.3233/JAD-161088.
  24. M. Oksanen *et al.*, “NF-E2-related factor 2 activation boosts antioxidant defenses and ameliorates inflammatory and amyloid properties in human Presenilin-1 mutated Alzheimer’s disease astrocytes,” *Glia*, vol. 68, no. 3, pp. 589–599, Mar. 2020, doi: 10.1002/glia.23741.
  25. R. J. Johnson *et al.*, “Could Alzheimer’s disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism?,” *Am J Clin Nutr*, vol. 117, no. 3, pp. 455–466, Mar. 2023, doi: 10.1016/j.ajcnut.2023.01.002.
  26. N. Lu *et al.*, “Gout and the risk of Alzheimer’s disease: a population-based, BMI-matched cohort study,” *Ann Rheum Dis*, vol. 75, no. 3, pp. 547–551, Mar. 2016, doi: 10.1136/annrheumdis-2014-206917.
  27. M. Perluigi, F. Di Domenico, and D. A. Butterfield, “Oxidative damage in neurodegeneration: roles in the pathogenesis and progression of Alzheimer disease,” *Physiol Rev*, vol. 104, no. 1, pp. 103–197, Jan. 2024, doi: 10.1152/physrev.00030.2022.
  28. R. P. Bhole, R. V. Chikhale, and K. M. Rathi, “Current biomarkers and treatment strategies in Alzheimer disease: An overview and future perspectives,” *IBRO Neurosci Rep*, vol. 16, pp. 8–42, Jun. 2024, doi: 10.1016/j.ibneur.2023.11.003.
  29. R. D. Haryuni *et al.*, “Elevated Serum Xanthine Oxidase and Its Correlation with Antioxidant Status in Patients with Parkinson’s Disease,” *Biomolecules*, vol. 14, no. 4, Apr. 2024, doi: 10.3390/biom14040490.
  30. E. R. et al Dorsey, “Global, regional, and national burden of Parkinson’s disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016,” *Lancet Neurol*, vol. 17, no. 11, pp. 939–953, 2018.
  31. A. Siderowf *et al.*, “Assessment of heterogeneity among participants in the Parkinson’s Progression Markers Initiative cohort using  $\alpha$ -synuclein seed amplification: a cross-sectional study,” *Lancet Neurol*, vol. 22, no. 5, pp. 407–417, May 2023, doi: 10.1016/S1474-4422(23)00109-6.
  32. X. Dong-Chen, C. Yong, X. Yang, S. Chen-Yu, and P. Li-Hua, “Signaling pathways in Parkinson’s disease: molecular mechanisms and therapeutic interventions,” *Signal Transduct Target Ther*, vol. 8, no. 1, p. 73, Feb. 2023, doi: 10.1038/s41392-023-01353-3.
  33. M. Bortolotti, L. Polito, M. G. Battelli, and A. Bolognesi, “Xanthine Oxidoreductase: A Double-Edged Sword in Neurological Diseases,” Apr. 01, 2025, *Multidisciplinary Digital Publishing*

Institute (MDPI). doi: 10.3390/antiox14040483.

34. V. Dias, E. Junn, and M. M. Mouradian, "The Role of Oxidative Stress in Parkinson's Disease," *J Parkinsons Dis*, vol. 3, no. 4, pp. 461–491, Nov. 2013, doi: 10.3233/JPD-130230.
35. G. Kuo, R. Kumbhar, W. Blair, V. L. Dawson, T. M. Dawson, and X. Mao, "Emerging targets of  $\alpha$ -synuclein spreading in  $\alpha$ -synucleinopathies: a review of mechanistic pathways and interventions," *Mol Neurodegener*, vol. 20, no. 1, p. 10, Jan. 2025, doi: 10.1186/s13024-025-00797-1.
36. L. A. Starr *et al.*, "Attenuation of Dopaminergic Neurodegeneration in a C. elegans Parkinson's Model through Regulation of Xanthine Dehydrogenase (XDH-1) Expression by the RNA Editase, ADR-2," *J Dev Biol*, vol. 11, no. 2, p. 20, May 2023, doi: 10.3390/jdb11020020.
37. R. D. Haryuni *et al.*, "Elevated Serum Xanthine Oxidase and Its Correlation with Antioxidant Status in Patients with Parkinson's Disease," *Biomolecules*, vol. 14, no. 4, p. 490, Apr. 2024, doi: 10.3390/biom14040490.
38. M. G. Battelli, L. Polito, and A. Bolognesi, "Xanthine oxidoreductase in atherosclerosis pathogenesis: Not only oxidative stress," *Atherosclerosis*, vol. 237, no. 2, pp. 562–567, Dec. 2014, doi: 10.1016/j.atherosclerosis.2014.10.006.
39. H. Yu *et al.*, "The clinical value of serum xanthine oxidase levels in patients with acute ischemic stroke," *Redox Biol*, vol. 60, p. 102623, Apr. 2023, doi: 10.1016/j.redox.2023.102623.
40. X. Chen *et al.*, "Machine Learning-Based Clinical Prediction Models for Acute Ischemic Stroke Based on Serum Xanthine Oxidase Levels," *World Neurosurg*, vol. 184, pp. e695–e707, Apr. 2024, doi: 10.1016/j.wneu.2024.02.014.
41. J. A. Singh and S. Yu, "Allopurinol and the risk of stroke in older adults receiving medicare," *BMC Neurol*, vol. 16, no. 1, p. 164, Dec. 2016, doi: 10.1186/s12883-016-0692-2.
42. S. Paganoni *et al.*, "Uric acid levels predict survival in men with amyotrophic lateral sclerosis," *J Neurol*, vol. 259, no. 9, pp. 1923–1928, Sep. 2012, doi: 10.1007/s00415-012-6440-7.
43. F. Zhang *et al.*, "Serum uric acid levels in patients with amyotrophic lateral sclerosis: a meta-analysis," *Sci Rep*, vol. 8, no. 1, p. 1100, Jan. 2018, doi: 10.1038/s41598-018-19609-2.
44. B. Iazzolino *et al.*, "High serum uric acid levels are protective against cognitive impairment in amyotrophic lateral sclerosis," *J Neurol*, vol. 271, no. 2, pp. 955–961, Feb. 2024, doi: 10.1007/s00415-023-12056-8.
45. A. S. Hari, M. C. Walker, and M. Patel, *Role of Reactive Oxygen Species in Epilepsy*. Oxford University Press New York, 2024. doi: 10.1093/med/9780197549469.001.0001.
46. E. Arhan *et al.*, "Effects of epilepsy and antiepileptic drugs on nitric oxide, lipid peroxidation and xanthine oxidase system in children with idiopathic epilepsy," *Seizure*, vol. 20, no. 2, pp. 138–142, Mar. 2011, doi: 10.1016/j.seizure.2010.11.003.
47. J. F. Stover, K. Lowitzsch, and O. S. Kempfski, "Cerebrospinal fluid hypoxanthine, xanthine and uric acid levels may reflect glutamate-mediated excitotoxicity in different neurological diseases," 1997.
48. M. Abdellatif, A. Ibrahim, M. Arafa, and A. Abdelazeim, "Nitric Oxide (NO), Xanthine Oxidase (XOD) and Malonylaldehyde (MAD) in children with seizures," *Zagazig University Medical Journal*, vol. 0, no. 0, pp. 0–0, Jan. 2020, doi: 10.21608/zumj.2020.19114.1615.
49. J. F. Stover, K. Lowitzsch, and O. S. Kempfski, "Cerebrospinal fluid hypoxanthine, xanthine and uric acid levels may reflect glutamate-mediated excitotoxicity in different neurological diseases," 1997.