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THE ROLE OF SEX-SPECIFIC FERROPTOSIS REGULATION IN THE PATHOGENESIS OF PARKINSON'S DISEASE

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Parkinson's disease is the second most common brain disorder worldwide, and one of its most puzzling features is that men develop it roughly 1.5 times more often than women. This pattern appears consistently across different countries and time periods, strongly suggesting real biological causes rather than chance or research bias. For decades, scientists have known that estrogen offers some protection to the brain. However, estrogen alone does not fully explain the male-to-female difference. In 2012, researchers discovered a completely new way cells can die, called ferroptosis. Unlike regular cell death, ferroptosis occurs when iron builds up inside cells and turns membrane fats rancid. The substantia nigra, which is the brain region that dies in Parkinson's disease, normally holds more iron than any other area. In Parkinson's patients, iron piles up even more there, creating perfect conditions for ferroptosis to occur. Dopamine neurons in this region are especially vulnerable because their normal work generates oxidative stress as a side effect.

When researchers examine sex differences in brain iron, the evidence is remarkably clear. Healthy men carry approximately 10 to 15 percent more iron in their substantia nigra than healthy women, and this difference begins early in life and never disappears. Several factors explain this gap. Estrogen helps women store iron in a safe, bound form attached to a protein called ferritin, which cannot participate in damaging reactions. Estrogen also reduces the number of transferrin receptors on cell surfaces, which are like doors that let iron into cells. Beyond hormones, women lose blood monthly for decades, which produces a measurable, lifelong reduction in total body iron by middle age. So, when Parkinson's pathology quietly begins brewing in the background, men have been stockpiling extra iron for years. Dopamine neurons in the substantia nigra are essentially sitting ducks for ferroptosis. They live in an iron-rich neighborhood, their normal work of creating dopamine generates oxidative stress as a side effect, and their membranes are loaded with the exact type of fats that go bad first during ferroptosis. A man's higher iron levels layered on top of this make those neurons even more vulnerable.

Estrogen fights ferroptosis through multiple mechanisms working together. It acts as a direct antioxidant within fatty membranes. It ramps up production of the enzyme glutathione peroxidase (GPX4) which cleans up damaged membrane fats. It increases ferritin levels to lock iron away safely. It reduces transferrin receptors to decrease iron entry into cells. Large studies confirm that postmenopausal women on estrogen therapy have roughly half the Parkinson's risk of non-users. For their reproductive years, women benefit from lower iron and active ferroptosis suppression. After menopause, when estrogen drops, that whole system fades.

Women typically develop Parkinson's symptoms about two years later than men. They are more likely to have the tremor-predominant form, which tends to be less aggressive. Men deal with more stiffness, more cognitive trouble, and more sleep disturbances. Brain scans show that healthy women have higher dopamine activity to begin with. Even medication responses differ women take lower doses but have more side effects. Men enter adulthood with higher brain iron that accumulates with age. Their dopamine neurons face decades of stress without estrogen protection.

The evidence strongly supports that sex differences in ferroptosis contribute to male predominance in Parkinson's disease. Men face nearly double the risk and carry more iron in their substantia nigra throughout life. Women benefit from lower iron loading and estrogen's anti-ferroptosis effects until menopause. The fact that estrogen therapy cuts Parkinson's risk by half proves this protection is real. These findings open the door for sex-specific prevention strategies. Future research should focus on iron reduction or ferroptosis blockers. Such approaches may work differently in males and females.