

# Retinal neurotoxicity of manganese exposure

<https://neurodegenerationresearch.eu/survey/retinal-neurotoxicity-of-manganese-exposure/>

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Manganese, neurotoxicity, Retinal, Circadian Rhythms, melanopsin

## Research Abstract

? DESCRIPTION (provided by applicant): Manganese (Mn) is a metal present in biological organisms in trace amounts and necessary for optimal functioning of many enzymes. Mn is found in industrial operations, in pesticides, in methylcyclopentadienyl manganese tricarbonyl (MMT), an anti-knock additive to gasoline, and in infant formula and parenteral nutritional formulations. Mn is homeostatically regulated, such that excess Mn is excreted in the bile, preventing Mn overload. However, this system can be saturated. With excessive exposure, toxic accumulation of Mn causes a form of Parkinsonism, known as manganism. While different areas of the brain are typically affected, manganism and Parkinson's disease (PD) share the

cardinal motor signs: bradykinesia, rigidity, postural instability and tremor. Additionally, the two conditions share non-motor symptoms, including depression, dementia, loss of sense of smell, reduced contrast vision, and various types of sleep disorders that precede motor symptoms by decades, such as difficulty falling asleep or staying asleep, rapid eye movement (REM) behavior disorder and circadian disruptions. Of these non-motor symptoms, sleep disruptions are the most common, affecting up to 90% of all PD patients, and a correspondingly large proportion of manganism patients. Patients report sleep disorders as a significant quality of life issue. Circadian regulation controls physiological activities including sleep, alertness and cognition by upregulating and downregulating genes in response to light. In the absence of light cues, the circadian system becomes decoupled from the 24-hour day, and affected genes and behaviors drift from normal 24-hour oscillations. In mammals, photoentrainment occurs when melanopsin (Opn4) is activated in the retina in the non-vision forming intrinsically photosensitive retinal ganglion cells (ipRGCs), which send projections to the suprachiasmatic nucleus (SCN), the master circadian oscillator in the brain. A transgenic mouse lacking melanopsin (Opn4 -/-) demonstrates defects in photoentrainment in response to light cues, though periodic oscillations in total darkness remain intact, indicating other inputs to the circadian system in mice. When crossed to mice with degeneration of rod and cone photoreceptors, circadian oscillations were completely lost. Given the connectivity of these cells, it is possible that rods and cones signal through ipRGCs even in the absence of melanopsin, and that loss of ipRGCs would mimic the Opn4 — photoreceptor loss phenotype with complete loss of photoentrainment. IpRGCs form gap junctions and synapses with dopaminergic (DAergic) amacrine cells. IpRGCs also function in contrast vision. Given that circadian photoentrainment and contrast vision are often disturbed in both manganism and PD, we propose melanopsin-dependent signaling through ipRGCs as a candidate mechanism underlying both symptoms. Numerous studies have used optical coherence tomography (OCT) to demonstrate thinning of the retina in PD patients, indicating cell loss in the inner nuclear layer (INL), the nerve fiber layer (NFL), and the ganglion cell layer (GCL)(Figure 1). Numerous types and subtypes of cells reside in these regions, including amacrine cells and ipRGCs (Figure 2). Dose-dependent retinal thinning has also been shown by magnetic resonance imaging (MRI) in mice following Mn injection. Notably, dopamine (DA) levels are reduced in both manganism and PD. The mechanism of DA cell loss is unknown. We hypothesize that circadian disruptions in both PD and manganism arise from loss of ipRGCs and/or amacrine cells. We propose to test this hypothesis by using a Mn-induced neurodegeneration model in the mouse to test for circadian disruption, as well as retinal Mn uptake, cell loss and transcriptional response to Mn. This work will have translational value in detecting early signs of manganism and PD that can be monitored noninvasively.

**Further information available at:**

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