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# CONSEQUENCES OF MANGANESE INTOXICATION ON THE CIRCADIAN REST-ACTIVITY RHYTHMS IN THE RAT

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**Abstract—Manganese (Mn) intoxication is associated with neurological dysfunctions collectively known as Parkinsonism or Manganism. Like in Parkinson's disease, Manganism is associated with motor disturbances, together with non-motor symptoms including cognitive and neuropsychiatric deficits. Although sleep dysfunctions are commonly reported among workers exposed to Mn, their underlying pathophysiology remains unknown. In this study, we investigated the rest-activity rhythms in rats treated daily with $MnCl_2$ (10 mg/kg, i.p) for 5 weeks. Locomotor activity was assessed under a light–dark (LD) cycle, constant darkness (DD) and during adjustment to 6 h shifts of the LD cycle. In LD conditions, Mn-treated rats exhibited a more fragmented and less stable rest-activity rhythm in addition to a reduction in the total 24-h amount of locomotor activity as well as in the activity confined to the active dark phase of the LD. Consequently, a significant decrease in the amplitude of the rest-activity rhythm was observed. These disturbances were displayed during and after Mn treatment. Furthermore, after the 6-h phase advance of the LD cycle, Mn-treated rats failed to re-adjust accurately their behavioral activity to the new shifted LD cycle. Upon release from LD into DD, Mn-treated rats expressed a normal and stable free-running period of their rest-activity rhythm (23.92 ± 0.07 h in Mn group vs. 24.01 ± 0.04 h in control rats). However, their rest-activity rhythm remained highly fragmented and less stable. Our results provide the first evidence that chronic Mn intoxication leads to impairment of rest-activity rhythms in addition to the motor and non-motor disturbances reported in Manganism.** **© 2016 IBRO. Published by Elsevier Ltd. All rights reserved.**

**Key words: manganese, circadian rhythm, rest-activity, light–dark cycles, entrainment, Parkinsonism.**

## INTRODUCTION

Manganese (Mn) is an essential ubiquitous trace nutrient that has important roles in multiple physiological functions (Aschner and Aschner, 2005). In humans and in animals in general, Mn functions as a necessary cofactor of several metalloid-enzymes crucial for normal neural and glial functions as well as enzymes involved in neurotransmitter synthesis and metabolism (Crossgrove and Zheng, 2004). Despite its essential role, excessive exposure to Mn in occupational settings or from the diverse environmental sources is associated with several health issues including anorexia, apathy, muscle and joint pain, memory loss, visual impairment, compulsive behavior, illusions and disorientation (Finkelstein et al., 2007). The most characterized and studied syndrome associated with Mn overexposure is usually referred to as Manganism or Mn-induced Parkinsonism (Guilarte, 2010). Phenotypically, this syndrome is characterized by a set of extrapyramidal symptoms resembling idiopathic Parkinson's disease (PD) resulting from progressive and permanent neurodegeneration of multiple brain structures (Guilarte, 2010).

As for PD, the non-motor aspects of Mn-induced Parkinsonism have not received their due scientific interest while the motor symptoms have received the lion's share of detailed investigations (Guilarte, 2010). Although not yet well described, sleep disturbances are among the most debilitating non-motor symptoms commonly reported in workers exposed to Mn (Bowler et al., 1999, 2007). The underlying neuropathophysiology behind this sleep dysfunction is still unknown.

Sleep/wake behavior is regulated by two distinct, yet inter-related physiological processes. A circadian process, based in the suprachiasmatic nucleus (SCN), is responsible for the timing of sleep and wake episodes, and a homeostatic process that tracts and responds to the quality and quantity of prior sleep and wakefulness (Achermann and Borbély, 2011). This dual homeostatic and circadian regulation of sleep/wake behavior implies that sleep alterations may arise as a

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*Abbreviations:* 5-HT, serotonin; BG, basal ganglia; DA, dopamine; DD, constant darkness; LD, light–dark; Mn, Manganese; NE, norepinephrine; NHP, non-human primate; PD, Parkinson's disease; SCN, suprachiasmatic nucleus; SNpc, substantia nigra pars compacta; SWS, slow wave sleep.

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consequence of a failure of one or both of these physiological processes. In the current study, we aimed to assess to what extent Mn intoxication affects the circadian system. To this end, we used a rat model repeatedly treated with Mn and investigated daily and circadian rhythms of rest-activity behavior under different light paradigms.

## EXPERIMENTAL PROCEDURES

### Animal housing and ethics statement

Twenty-eight adult male Wistar rats obtained from the animal breeding colony of the Faculty of Sciences of Rabat (Mohammed-V University of Rabat, Morocco), weighing between 250 and 280 g at the beginning of the experiment were used in the present study. Animals were singly housed in Plexiglas cages in a temperature-controlled room (21 ± 2 °C) with timed control of light cycles and free access to food and water. Before treatment, rats were housed under 12-h/12-h light–dark (LD, light on at 06:00 h) cycle and were handled daily and allowed to habituate to their home cages for at least 2 weeks. Light was supplied by fluorescent tubes (Philips, fluotone TLD 18W/54), providing an even 300-lux intensity light at cage level. All experiments with rats were carried out in conformity with principles of animal care (Portaluppi et al., 2010) in accordance with European Communities Council Directive 2010/63/EU. All efforts were made to minimize animal suffering.

### Mn treatment

The rats were randomly assigned to two separate groups: treated animal group ($n$ = 16) received between 09:00 and 10:00 h a daily intraperitoneal (i.p) injection of manganese chloride tetrahydrate ($MnCl_2{\cdot}4H_2O$, Sigma–Aldrich, St. Louis, MO, USA) dissolved in saline (NaCl, 0.9%) at the dose of 10 mg/kg during 5 weeks. The control group ($n$ = 12) received an equal volume of saline in the same conditions. The choice of i.p Mn administration compared to oral administration through drinking water is related to the possibility of controlling precisely the daily doses administered which should be the same for all the treated animals.

### Assessment of rest-activity rhythms

Daily locomotor activity rhythms were assessed by continuously monitoring locomotor activity using infrared motion detectors placed over the cages and a computerized data acquisition system (Circadian Activity Monitoring System, INSERM, Bron, France). Activity records were displayed as actograms and average waveforms. Locomotor activity rhythms, circadian entrainment and endogenous circadian activity were assessed using a series of different light regimes during and after Mn treatment. The overall timeline of the entire experimental protocol is shown in Fig. 1. All animals started with 5 weeks in a 12-h light: 12-h dark

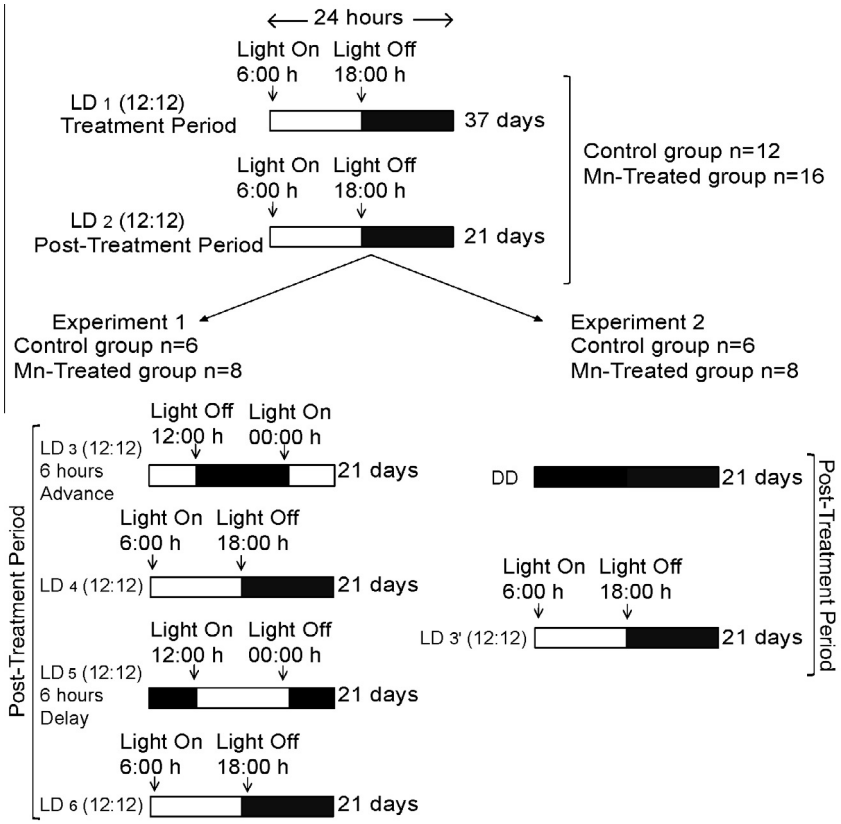


**Fig. 1.** Schematic representation of the experimental design depicting the sequential photoperiods that the rats were subjected to (top to bottom) and the number of days under each photoperiod. Light phase is depicted by a white bar, while the dark phase is shown by a black bar. The numbers in brackets refer to the number of hours of either light or dark, and the times refer to local clock time when the lights were either switched on or off.

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