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Manganese does not potentiate the neurotoxicity of MPTP金 良昊¹、Baek Sun Yong²、Kim Young Hoon³、朴 正鮮⁴¹Department of Occupational and Environmental Medicine Ulsan University Hospital,²Busan University Hospital, ³Medical College, Inje University, ⁴韓国産業安全公団

The importance of environmental agents such as manganese (Mn) and pesticides in the etiology of Parkinson's disease (PD) is gaining recognition. However, data on the role of Mn as a risk factor for PD is contradictory. Animal model data on the contribution of Mn to the development of parkinsonism is also contradictory. We utilized a mice model of parkinsonism to: (1) evaluate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity; (2) evaluate whether Mn exposure can affect MPTP-induced neurotoxicity.

The present study utilized a MPTP mice model of parkinsonism and a 2 × 3 experimental design (MPTP × ±Mn) as follows: SS; MPTP(-) × Mn(-); SLMn, MPTP(-) × low Mn(+); SHMn, MPTP(-) × high Mn(+); MpS: MPTP(+) × Mn(-); MpLMn, MPTP(+) × low Mn(+); MpHMn, MPTP(+) × high Mn(+) (Each group contained seven to ten mice.)

Male C57BL/6 mice (8 weeks old, body weight 25-30 g) were caged in an air-conditioned room maintained at 22±2 °C, relative humidity 50 ± 10%, with a 12/12 h light/dark cycle. We administered MPTP to MpS, MpLMn, and MpHMn group via an intraperitoneal injection of 20mg/kg/day four times every two hours. The SS, SLMn, and SHMn group received the same volume of saline intraperitoneally. After that, MpLMn and SLMn group were treated intraperitoneally with 0.2 ml of MnCl₂·4H₂O (2mg/kg body weight), and the MpHMn and SHMn group were treated with 0.8 ml of MnCl₂·4H₂O (8mg/kg body weight) once a day for 3 weeks. The SS group received the same volume of saline intraperitoneally. After the last Mn injection, the mice were sacrificed.

Blood Mn levels were elevated in the Mn-exposed groups. The number of tyrosine hydroxylase (TH)-immunoreactive (ir) neurons in the substantia nigra pars compacta (SNpc) were decreased significantly in the MPTP-exposed groups (MpS, MpLMn and MpHMn) in comparison with non-exposed groups (SS or SLMn, SHMn). The densities of TH-ir axon terminals in caudate-putamen (CPU) were significantly decreased in MPTP-treated groups, compatible with a decrease of TH-ir neurons in the SNp. However, Mn treatment did not affect the densities of TH-ir axon terminals in the CPU nor the number of TH-ir neurons in the SNpc.

MPTP treatment resulted in a reactive astrocytosis, which was shown as a profound increase in GFAP immunoreactivity in the CPU or globus pallidus (GP). The densities of GFAP-ir astrocytes in the CPU or GP were significantly increased in the MPTP-treated groups in comparison with MPTP non-treated groups. But, Mn treatment did not affect MPTP neurotoxicity.

Concentrations of dopamine (DA) in the corpus striatum were decreased significantly in the MPTP-exposed groups only, but Mn had no effect. DA reduction was 85-90%. Concentrations of DA metabolites such as 3,4-dihydrophenylacetic acid (DOPAC) and homovanillic acid (HVA) in the corpus striatum were also decreased significantly in MPTP-exposed groups only, showing a similar pattern to those of DA (the reduction was approximately 60 %). Thus, decreased dopaminergic activities with MPTP led to decreased DA and its metabolites. In summary, MPTP targeted dopaminergic systems whereas Mn does not potentiate the neurotoxicity of MPTP.