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Chelation therapy of manganese intoxication with para-aminosalicylic acid (PAS) in Sprague–Dawley rats

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Para-aminosalicylic acid (PAS), an FDA-approved anti-tuberculosis drug, has been used successfully in the treatment of severe manganese (Mn)-induced Parkinsonism in humans [Jiang Y-M, Mo X-A, Du FQ, Fu X, Zhu X-Y, Gao H-Y, et al. Effective treatment of manganese-induced occupational Parkinsonism with paminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006;48:644–9]. This study was conducted to explore the capability of PAS in reducing Mn concentrations in body fluids and tissues of Mn-exposed animals. Sprague–Dawley rats received daily intraperitoneally (i.p.) injections of 6 mg Mn/kg, 5 days/week for 4 weeks, followed by a daily subcutaneously (s.c.) dose of PAS (100 and 200 mg/kg as the PAS-L and PAS-H group, respectively) for another 2, 3 or 6 weeks. Mn exposure significantly increased the concentrations of Mn in plasma, red blood cells (RBC), cerebrospinal fluid (CSF), brain and soft tissues. Following PAS-H treatment for 3 weeks, Mn levels in liver, heart, spleen and pancreas were significantly reduced by 25–33%, while 3 weeks of PAS-L treatment did not show any effect. Further therapy with PAS-H for 6 weeks reduced Mn levels in striatum, thalamus, choroid plexus, hippocampus and frontal cortex by 16–29% ($p < 0.05$). Mn exposure greatly increased iron (Fe) and copper (Cu) concentrations in CSF, brain and liver. Treatment with PAS-H restored Fe and Cu levels comparable with control. These data suggest that PAS likely acts as a chelating agent to mobilize and remove tissue Mn. A high-dose and prolonged PAS treatment appears necessary for its therapeutic effectiveness.

Keywords: Para-aminosalicylic acid or PAS, Manganism, Manganese, Iron, Copper, Chelation cerebrospinal fluid, Choroid plexus, Striatum