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Manganese exposure induces hyperactivity and dopaminergic dysfunction in young C57Bl/6 mice

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Introduction: Introduction. Attention-Deficit/Hyperactivity Disorder (ADHD) is estimated to affect up to 9% of the population. While genetic variation is a critical aspect of the etiology, environmental factors including toxicant exposure via air pollution and contaminated water greatly impacts the genotype-phenotype relationship. Manganese (Mn) is a required mineral, ubiquitous in our diets and typically well-regulated. However, chronic high exposure is linked to neurodegenerative disorders and dysregulated cellular functioning. Developing brains may be even more sensitive to environmental toxins like excess Mn.

Methods: Methods. Male and female C57Bl/6 mice were chronically exposed to Mn via a control (70 ppm) or high Mn (2400 ppm) diet from weaning through 12 weeks of age, or acutely exposed via three subcutaneous injections of 50 mg/kg MnCl2-tetrahydrate over 7 days at 6-8 weeks of age. Behavioral testing was conducted to measure changes in exploratory locomotor activity in a novel environment, anxiety-like behavior in the elevated zero maze, repetitive behaviors (marble burying), and changes in nest building ability. Brain Mn levels were confirmed by mass spectrometry and key proteins in striatal dopaminergic function were assayed by Western blot.

Results: Results. Both dietary and systemic treatments significantly elevated brain Mn. Both treatments also led to increased activity in locomotor activity chambers, although this effect was observed exclusively in females following dietary Mn administration. Following high dietary Mn brain weight was slightly but significantly decreased by 2-3% in females only. Expression of the dopamine transporter (DAT), Tyrosine hydroxylase (TH) and phosphorylated tyrosine hydroxylase (pTH) were all increased in female striatum following Mn exposure, although the TH:pTH was lower than controls. The same pattern of changes was not observed in male mice suggesting sex-specific dysregulation of dopaminergic function.

Discussion: Discussion. Excess Mn via two distinct exposure routes led to dysregulation of dopaminergic function and clear behavioral differences in mice that were more prominent in female mice than males. The data highlight the potential for environmental exposure to metals such as Mn to directly impact child brain health and development with clear adverse behavioral outcomes. The data also clearly highlight the need for developmental and toxicological studies to be conducted in both male and female animals.

Keywords:
Hyperactivity, Manganese, Dopamine