Sex-specific modulation of juvenile midbrain dopamine expression by perinatal serotonin

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Background

Both prenatal and neonatal hyperserotonemia have been documented as risk factors for autism spectrum disorder (ASD). In humans, mothers taking SSRIs prescribed during pregnancy are more likely to have children with ASD (Andalib et al., 2017). The serotonin agonist 5-methoxytryptamine (5-MT) has been commonly used to induce perinatal hyperserotonemia in rats; daily injections of 5-MT into pregnant rodent dams and then into their pups upon birth (~E12–P20) can induce ASD-like symptoms, such as social deficits, sensory hyper-responsiveness, and coordination deficits, in juveniles and adults (Madden and Zup, 2014; Martin et al., 2012; Whitaker-Azmitia, 2005).

Although perinatal 5-MT has been shown to affect the development of numerous neurochemical networks, its influence on dopaminergic neurons are not understood. Given the importance of dopamine neurotransmission for many of these behaviors 5-MT influences, we explored the effects of perinatal hyperserotonemia on the number of dopamine neurons in the substantia nigra (SN), ventral tegmental area (VTA), AVPV of the hypothalamus, and zona incerta (ZI) which are important for movement, motivation, reproductive behavior, and sensory integration, respectively. Our results could lead to a better understanding of ASD's pathophysiology.

Methods

Treatments

- Either 5-MT (1 mg/kg) or a saline vehicle was injected into pregnant Long-Evans rat dams daily beginning at day 12 of gestation.
- After birth, all pups in each litter continued to receive the same treatment daily until P20.
- At P21, pups were weaned from the dam into same-sex sibling groups.
- Perfusions were conducted and brains were collected on postnatal day 30–32.

Histology

- Brains were processed immunohistochemically for tyrosine hydroxylase (TH; to show location of dopaminergic cells).
- For each brain area, cells expressing TH were counted (bilaterally) and summed from 3 consecutive sections.
- Two-way ANOVAs (sex x treatment) were used to analyze data.

Results

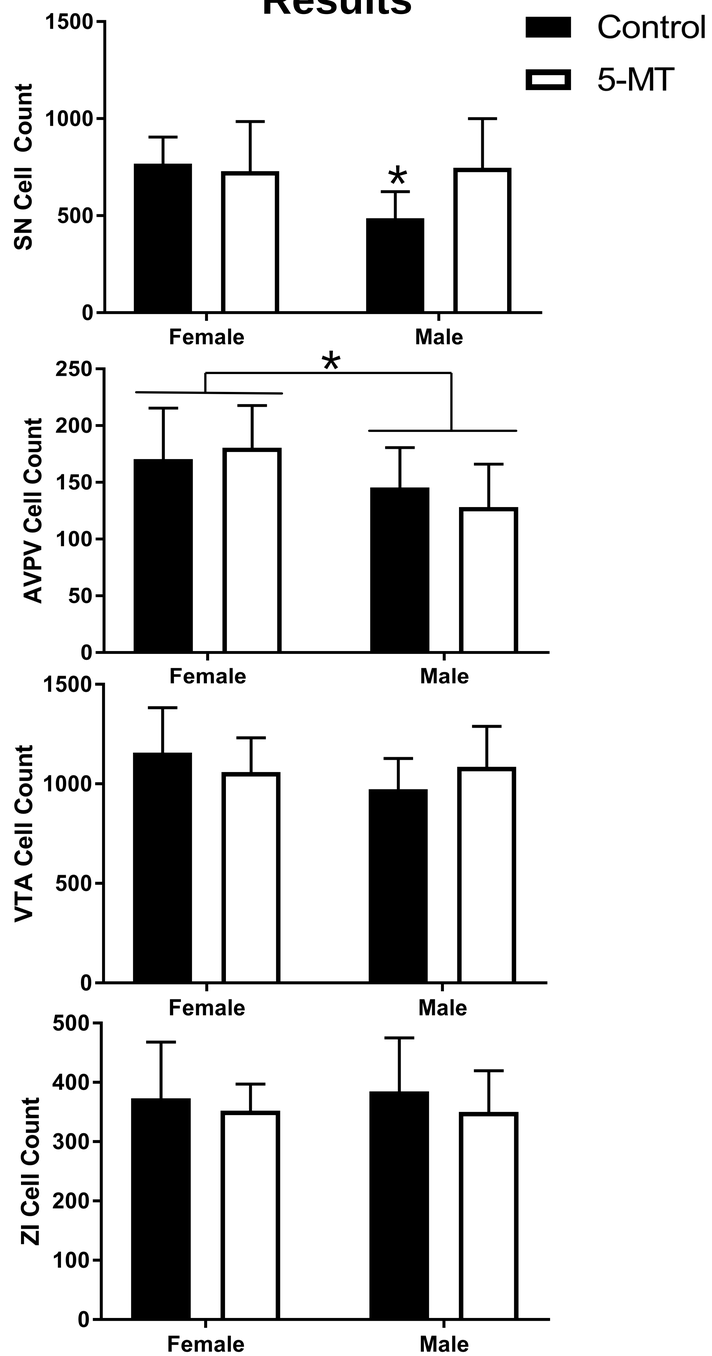

Figure 1. Effects of perinatal 5-MT treatment on the number of dopaminergic cells in the SN, AVPV, VTA, and ZI.

Summary and Conclusions

- 5-MT selectively increased the number of TH-positive cells in the SN, but only in males. Alterations in dopamine transmission may help explain 5-MT-induced coordination and movement deficits.
- 5-MT treatment has also been shown to have sex-specific effects on 5-HT and oxytocin neurons in the hypothalamus and on play behavior (Madden and Zup, 2014), although the mechanisms underlying these sex differences are not understood.
- ASD is more common in boys than girls, and a differential sensitivity to perinatal conditions, particulatly in the SN, may help explain this.
- Although we were surprised to observe a sex difference in the SN among control animals, this may be a consequence of handling the newborn rats every day, particularly given that neonatal handling affects serotonin turnover (Smythe et al., 1994).
- We observed the well-documented sex difference in the AVPV, but this was not influenced by 5-MT treatment. Furthermore, neither sex nor treatment had an effect on the number of dopaminergic neurons in the VTA or ZI.
- Animal models of Parkinson's Disease using rotenone or MPTP show SN-specific effects, so perhaps a similar mechanism is at play (Lu et al., 2018)

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