Title

The Role Of Histone Acetylation In Sexual Differentiation Of The Mouse Brain

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Abstract

Sex differences are widespread throughout the nervous system and have been identified in relation to almost every neural characteristic, from basic anatomy, to behavior, to differences in the prevalence of neuropathology. Most sex differences arise following exposure to the steroid hormone, testosterone, but relatively little is known about the molecular mechanism of steroid hormone action. In many cases, perinatal hormone exposure determines life-long sex specific changes, suggesting a long-lasting cellular memory for the testosterone exposure. Testosterone-induced changes in chromatin structure could account for this memory leading to long-term changes in gene expression. In this dissertation, I tested the hypothesis that chromatin remodeling plays a role in sexual differentiation of brain morphology, neurochemistry and behavior. To test this, I disrupted the balance between histone acetylation and deacetylation using the histone deacetylase inhibitor, valproic acid (VPA), during the critical period for hormone action. First, I determined that VPA treatment increased histone acetylation 24 hours following injection. Next, I revealed that masculinization of BNSTp volume and cell number is blocked by neonatal VPA treatment. I then determined the effect of VPA treatment on cell death in the BNSTp. As expected, females had more dying cells than males. However, VPA treatment had no effect on cell death in either sex. Testosterone treatment reduced cell death in the BNSTp of females and VPA treatment prevented this testosterone-induced cell survival. In the AVPV, females had more TH-positive cells than males but VPA treatment did not affect the number of TH cells in either sex. In the lateral septum, the predicted sex difference was observed; males had more vasopressin-immunoreactive fibers than females. VPA treatment had no effect in males but increased the vasopressin fiber density in females, reducing the sex difference. In addition, males showed a preference for female-soiled bedding whereas females showed a preference for male-soiled bedding. VPA treatment did not alter olfactory preference in males, but decreased preference for male bedding in females, partially masculinizing females. Taken together, these results suggest that regulation of histone acetylation following testosterone exposure plays a role in sexual differentiation of brain morphology, neurochemistry and behavior.

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