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EPIGENETICS

From father to son

Prenatal stress influences adult cognition and behaviour, effects that are mediated, at least in part, by epigenetic changes. Morgan and Bale now show that the effects of prenatal stress on the masculinization of the brain can be transmitted to subsequent generations by epigenetic mechanisms.

Previous studies have shown that stress during early gestation can dysmasculinize the behaviour of male mice (dysmasculinize is used to mean a reduction in masculinity). Here, the authors compared the male offspring of male mice exposed to prenatal stress (F2-S mice; F2 refers to the second generation of mice) with male offspring of control males (F2-C mice) to determine whether these effects could be transmitted to a second generation.

The F2-S mice exhibited some dysmasculinized behaviour: in the tail suspension test their behavioural stress response was much stronger than that of F2-C mice, and more similar to that of females. Furthermore, the brains of F2-S mice also exhibited dysmasculinization: in the tail suspension test they exhibited a stronger behavioural stress response — similar to that of females — than F2-Cs. The sexual dimorphism of the male brain is programmed during a critical period in late gestation by a surge of testosterone that is converted to oestrogen in the brain. The authors observed an upregulation in the expression of oestrogen receptors that mediate the effects of this oestrogen in F2-S mice. They suggest that these mice may have had reduced exposure to these programming hormones during gestation.

The authors also found that three microRNAs (miRNAs) that usually have sexually dimorphic expression were expressed at 'female' levels in F2-S mice. Additional evidence for a role for miRNAs in masculinizing the brain was provided: administration of an aromatase inhibitor, which prevents the conversion of testosterone to oestrogen, to newborn male mice altered the brain miRNA expression pattern so that it was indistinguishable from that of females. This suggests a molecular mechanism by which oestrogen acts to masculinize the brain.

This study supports previous work showing that prenatal stress effects are transmitted down the paternal lineage. The work implies that epigenetic changes, presumably in the male germ cells, alter exposure to the hormones that mediate brain masculinization. It may provide insight into the heritability and pathophysiology of sex-biased neurodevelopmental disorders such as autism.

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ORIGINAL RESEARCH PAPER Morgan, C. P. and Bale, T. L. Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. *J. Neurosci.* **31**, 11748–11755 (2011)