EPIGENETICS

Stressed for life

Early-life stress (ELS) has long-lasting effects on the brain, and the epigenetic mechanisms underlying them are beginning to be unravelled. Murgatroyd *et al*. now show that methyl-CpG-binding protein 2 (MeCP2)-mediated regulation of arginine vasopressin (*Avp*) gene expression in parvocellular hypothalamus neurons contributes to the phenotype induced by maternal separation in mice.

As in previous studies, daily 3-hour separation of mouse pups from their mother persistently altered the offspring's hormonal and behavioural responses to stress; this included elevated *Avp* mRNA levels in the hypothalamus. Importantly, treatment with an AVP V1b receptor antagonist reversed the mice's increased stress responses and impaired memory, indicating a central role for AVP in the ELS phenotype.


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Investigating how ELS might increase hypothalamic *Avp* expression, the authors found that the *Avp* enhancer region was persistently hypomethylated at five CpG residues in hypothalamus tissue of ELS mice, and that methylation levels correlated negatively with *Avp* mRNA levels.

Methylated DNA is targeted by MeCP2, leading to gene silencing; indeed, treating a mouse hypothalamic cell line with a methylation inhibitor reduced MeCP2 binding at the methylation-sensitive enhancer and increased *Avp* transcription. MeCP2 can be dissociated from methylated DNA through activity-dependent phosphorylation by CaMKII. Accordingly, transfecting the cells with CaMKII or depolarizing them reversed MeCP2-mediated repression of *Avp*.

Does reduced MeCP2 binding underpin the ELS-induced increase in *Avp* expression? The authors found that immediately after the end of ELS, MeCP2 phosphorylation was increased and MeCP2 binding to the *Avp* enhancer was reduced, whereas *Avp* enhancer methylation levels were unaltered in hypothalamus neurons. By contrast, 6 weeks later, MeCP2 phosphorylation was normalized but key residues of the *Avp* enhancer were hypomethylated. This suggests that ELS dynamically regulates *Avp* expression, initially through MeCP2 phosphorylation and later through hypomethylation of the *Avp* enhancer.

This study shows that phosphorylation and binding of MeCP2 might be a means by which experience drives persistent changes in gene expression, and that *Avp* is an important target for epigenetic regulation by adverse early-life events.

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ORIGINAL RESEARCH PAPER Murgatroyd, C. *et al.* Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nature Neurosci.* 8 Nov 2009 (doi:10.1038/nn.2436)
FURTHER READING Lupien, S. J. *et al.* Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Rev. Neurosci.* **10**, 434–445 (2009)