NEUROGENETICS

Undoing epigenetics

Maternal behaviour during development can have a powerful influence on stress levels of the offspring later in life as a result of lasting epigenetic modifications. According to work published in *The Joural of Neuroscience*, it now seems that just as gene expression can be altered during development, it can also be altered later in life to reverse these modifications.

Stress responses are mediated by regulation of the hypothalamic–pituitary–adrenal (HPA) axis: neural stimulation causes release of corticotropin-releasing factor (CRF), which activates the HPA axis, whereas glucocorticoid feedback blocks synthesis and release of CRF, thereby reducing HPA responses to stress.

Adult rats that have experienced high levels of maternal care — measured by the extent of licking and grooming behaviour — during the first week of life have reduced levels of hypothalamic CRF and lower HPA responses to stress in adulthood compared with those that have received relatively low levels of maternal care early in development. Cross-fostering studies suggest that this effect is due to maternal behaviour and not to genomic transmission of stress responses. The epigenetic mechanism that underpins these differences involves changes in the methylation state of the hippocampal glucocorticoid receptor promoter: in animals that have received high levels of maternal care, this promoter is hypomethylated, whereas lower levels of maternal care are associated with hypermethylation of this promoter.

To test the possibility that these DNA methylation patterns can be reversed, Weaver and colleagues infused methionine — a well-known dietary modulator of DNA methylation — into the brains of adult rats that had received either high or low levels of maternal care. Increased methionine levels induced hypermethylation of the glucocorticoid receptor promoter in rats that had received high levels of maternal care, which did indeed reverse the effects of maternal behaviour in early development on glucocorticoid receptor expression and the HPA response to stress in adult life. These results suggest that the enzymatic mechanisms that underlie DNA methylation and demethylation can be activated not only during development but also in adult postmitotic hippocampal neurons. Stable epigenetic changes therefore seem to be susceptible to plasticity in adulthood.

Dietary methionine is essential for normal brain development, and abnormalities in DNA methylation have been linked to some neurological disorders, such as fragile X syndrome, and several psychiatric conditions, including schizophrenia. As Weaver *et al.* speculate, these data raise the intriguing possibility that epigenetic modifications during development and adulthood could be influenced by dietary modification of methylation, and might offer a potential therapeutic avenue for the treatment of a range of disorders of the nervous system.

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ORIGINAL RESEARCH PAPER Weaver, I. C. G. *et al.* Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. *J. Neurosci.* **25**, 11045–11054 (2005)