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Journal

Endocrinology, 155(5)

ISSN

0888-8809

Author

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Publication Date

2014-05-01

DOI

10.1210/en.2014-1267

Peer reviewed

Early Life Stress: Nature and Nurture

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Recent and still nascent understanding of epigenetic marks, how they occur and are modified, has been an enormous boon to studies in the fields of endocrinology and neuroscience. Because the genetic DNA sequence does not usually change during the lifetime of the individual, it had been difficult to understand how marked and persistent changes in gene transcription rates occur in response to changes in the environment and experiences of the individual. Although not the only mechanism, hiding and exposing regulatory transcription sites on DNA through epigenetic changes in chromatin folding and unfolding allow much of the great flexibility that we observe occurring in biological processes.

Methylation of cytosine residues in cytosine-phosphoguanine dinucleotides is known to result in either silencing or augmenting gene activity (see Figure 1) (1, 2). Methylated DNA can be bound by methyl-CpG-binding domain proteins. Methyl-CpG-binding domain protein then recruits additional proteins to the locus, such as histone deacetylases and other chromatin remodeling proteins that modify histones, thereby forming compact, inactive chromatin, making genes inaccessible for transcription. The link between DNA methylation and chromatin structure is very important. In particular, loss of methyl-CpG-binding protein 2 (MeCP2) has been implicated in Rett syndrome (3).

In an article published in this issue of *Endocrinology*, Wu et al (4) show that the long-lasting effects of early life stress (ELS) in mouse pups that result in increased pituitary proopiomelanocortin mRNA, ACTH and corticosterone secretion are mediated by the reduction of methylation in a specific CpG site on the distal *POMC* promoter (4). Methylation of the CpG 6–8 site was shown to reduce *POMC* activity in vitro and in vivo and was accompanied by high levels of MeCP2, which selectively bound the CpG

6–8 methylation site. MeCP2 recruits corepressors to decrease *POMC* gene activity. The effect of methylation in CpG sites on transcription, in this case, is inhibitory. The authors did a very thorough job in determining the effects of ELS on pituitary *POMC* synthesis, although they did not determine what cellular event initiated the hypomethylation and low MeCP2 at the CpG6–8 site.

However, hypomethylation of the distal *POMC* promoter is just one effect of ELS on gene methylation and on regulation of the hypothalamo-pituitary-adrenal axis, as the authors showed in an earlier study on the brains of the same mice that had been subjected to neonatal stress (5). In that study, they found that, through acting at a specific CpG methylation site, MeCP2 persistently down-regulated *Avp* expression in parvocellular cells in the paraventricular nuclei (PVN). ELS decreased MeCP2 binding to methylcytosines in the promoter region but did not alter DNA methylation. In this case, the authors show that it was likely that neuronal activity resulted in Ca^{++} -dependent phosphorylation of MeCP2 which reduced its binding to specific methylated cytosines. There was no effect on corticotropin-releasing factor mRNA (5). That is both interesting and somewhat surprising, because there are high levels of MeCP2 in parvocellular neurons in the PVN, and mice bearing a truncated MeCP2 gene (*Mecp2*^{308/Y}) have elevated CRF mRNA in the PVN, amygdala, and bed nuclei of the stria terminalis (6).

Earlier studies have shown that the effect of ELS on CRF expression depends on the control group that is used to compare with the group exposed to 3 hours per day of maternal separation (7–9). In untouched, unhandled litters, which was the control group in Refs. 4, 5, adults have similar CRF expression levels compared with rats exposed to ELS of 3-hour separation. However, if the reference control group is either animals experiencing normal vi-

ISSN Print 0013-7227 ISSN Online 1945-7170

Printed in U.S.A.

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Received March 27, 2014. Accepted March 31, 2014.

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Abbreviations: ELS, early life stress; MeCP2, methyl-CpG-binding protein 2; PVN, paraventricular nuclei.

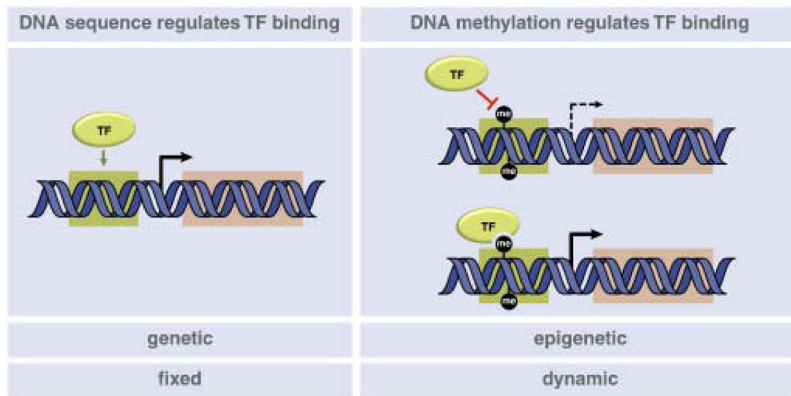


Figure 1. Coordinate genetic and epigenetic mechanisms regulate transcription factor (TF) binding. Left, TF binding to cognate DNA sequence motifs (yellow box) regulates transcriptional output (orange box). Right, TF binding to methylated DNA sequence motifs (black circles) both positively and negatively regulates transcriptional output (1). Figure 2 reprinted from Rothbart and Strahl (1), with permission from Elsevier.

varium treatment or 15 minutes of handling daily, CRF expression is elevated in the adult ELS rats in the amygdala, bed nuclei of the stria terminalis, and PVN (7, 8), suggesting that the DNA methylation state and MeCP2 may differ between entirely unhandled controls and animals handled by vivarium staff during routine cage maintenance, or removed from mothers for 15 minutes per day for the first 2 weeks of life. The difference between the groups with higher or normal CRF expression in the PVN appears to be the amount and intensity of high licking and grooming provided to the neonatal pups by the mothers (9).

ELS causes long-term changes throughout the entire brain, not only in components of the HPA axis, probably primarily through epigenetic mechanisms (10, 11). The most common ELS that has been studied in rodents is repeated bouts of prolonged separation from the mother during the first 2 weeks of life. The fact that the stressor occurs early in life, while the brain and body are develop-

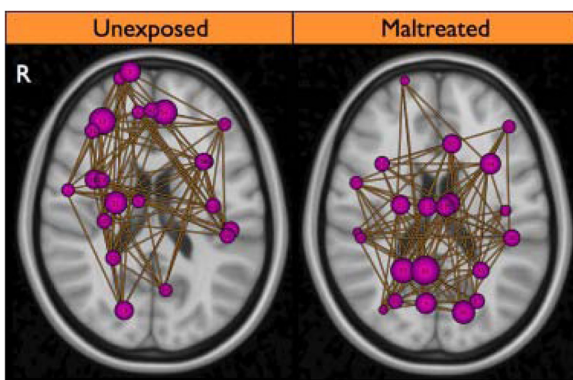


Figure 2. Rich-club networks in healthy unexposed control subjects and individuals with maltreatment histories. The maltreated rich clubs were selected to contrast with the control network in either minimum number of required direct connections ($k = 1/4 \cdot 21$) or number of total nodes ($k = 1/4 \cdot 19$). Node size was scaled by eigenvector centrality. Figure 3 reprinted from Teicher et al (28), with permission from Elsevier.

ing, suggests that this may be a critical period during which normal growth and wiring of the brain is profoundly affected. Certainly, there is a great deal of evidence from exposing experimental animals to ELS that marked changes in learning, memory, activity in the HPA axis, and behavior exist, and, in various brain sites, epigenetic marks linked to ELS have been shown to be present in the adult, including hubs related to memory, like the hippocampus (12, 13), prefrontal cortex (14), and hubs related to motivation, like the nucleus accumbens (15).

Does the animal work on ELS translate to the human being? It seems likely that it does, although it is very early days for a definitive answer. Differences in epigenetic marks between DNA in lymphocytes from monozygotic twins, both in DNA methylation and histone acetylation, are discordant, and there are increasing differences with age, suggesting that environmental influences are important to the discordance (16). Certainly, ELS in people causes many of the same behavioral (anxiety in people and anxiety-like behavior in animals, depression in people, depression-like behavior in rodents) and HPA axis effects that are seen in animal models (17–20). Although there are only very few studies in human beings on the effects of ELS on epigenetic marks, these suggest that, in people as in rats and monkeys, a history of early maltreatment leaves strong epigenetic traces in adults (for reviews, see Refs. 21, 22 and a very interesting opinion piece about interactions between ELS and nutrition on hippocampal epigenetic marks in Ref. 23). Childhood adversity is associated with epigenetic alterations in the promoters of several genes in hippocampus, collected postmortem (24–26). Furthermore, in hippocampi from suicides with childhood abuse compared with suicides without child abuse, methylation of the glucocorticoid receptor gene (*NR3C1*) was increased in the promoter region and glucocorticoid receptor mRNA was decreased (25).

It is not known whether there is a cascade of epigenetic markers that are placed throughout multiple brain sites as a consequence of a single epigenetic change in neurons at one brain site that then informs the rest of the brain as a consequence of neural activity and Calmodulin-dependent protein kinase II activity, or whether the multiple sensory inputs associated with ELS stimulate epigenetic marks in various neuronal hubs, which then cascade throughout networks in the rest of the brain. In early stud-

ies by Levine's group, it was shown that stroking and feeding reduced HPA responses in neonatal rats to a 12-hour period of maternal deprivation (27). It is unknown whether stroking and feeding resulted in epigenetic changes, or whether the effects persisted until adulthood. However, it seems more likely that several brain sites respond to the sensory input (or its lack) determined by ELS, rather than a single responsible site. Further animal work is needed to get a handle on this.

However, whether it is a single site that results in a cascade of effects or multiple sites, the adult outcome of childhood maltreatment in people results in a very different set of neural networks acting on behaviors of the adults. Downstream of epigenetic changes in neurons is neuronal network function. This has been examined in groups of 18- to 25-year-old maltreated or neglected children and nonmaltreated controls by magnetic resonance imaging and network analysis of cortical thickness measures (28). When hubs of a network tend to be more densely connected among themselves than to lower-degree nodes, they are a "rich club." Rich clubs were primarily frontal and temporal in controls and primarily occipital and temporal in the maltreated network; only 3 of 22 nodes had a high probability of membership in both rich clubs (see Figure 2).

Based on these results, the authors concluded that ELS "was associated with decreased centrality in regions associated with emotion regulation and ability to accurately attribute thoughts or intentions to others, and with enhanced centrality in regions involved in internal emotion perception, self-referential thinking, and self-awareness. This may provide a potential mechanism for how maltreatment increases risk for psychopathology." (28). If these effects of maltreatment rest on differences in epigenetic marks laid down during childhood maltreatment, we have a very long way to go to fully explicate what happens in the brain (and body) after ELS.

However, finding out what is going on with epigenetic changes in different sites in abundant detail will probably be very important, because there are hints that the effects of ELS can be ameliorated by environmental enrichment in postweanling rats (29), there is clearly resilience as well vulnerability to stress via epigenetic mechanisms (30), and methylation of CpG islands in DNA is reversible (31). It is possible that treatments that promote resilience after ELS will eventually include pharmaceutical manipulation of specific epigenetic marks that may be critical to resilient responses to that maltreatment.

Acknowledgments

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Disclosure Summary: The author has nothing to disclose.

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