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Stress-induced early-life epigenetic changes influence resilience or vulnerability to stress later in life

Abstract:

Stressful events in early life might lead to stress resilience or vulnerability throughout life. During the critical developmental period of thermal-control establishment, heat stress was found to affect both body temperature and expression of CRH in the hypothalamic paraventricular nucleus. Both increased during heat challenge in chicks that were trained to be vulnerable to heat, whereas they decreased in chicks that were trained to be resilient. Accordingly, DNA CpG methylation (5mC) and hydroxymethylation (5hmC) at the CRH intron, which we found to serve as a repressor element, displayed low 5mc% alongside high 5hmc% in resilient chicks, and vice versa in vulnerable ones. REST, which has a binding site on this intron, bound abundantly during acute stress and was nearly absent during moderate stress, restricting repression by the repressor element activating CRH gene transcription. Furthermore, REST assembled into a protein complex with TET3, which bound directly to the CRH gene. Finally, the histone acetylation enzyme GCN5 was recruited to this complex, increasing H3K27 acetylation during harsh, but not moderate heat conditioning. We conclude that an epigenetic mechanism involving both post-translational histone modification and DNA methylation in a regulatory segment of CRH is involved in determining a resilient or vulnerable response to stress later in life.