W52. Early-Life Experience Reprograms Stress-Sensitive Neurons and Influences Adult Phenotype via NRSF/REST-Dependent Epigenetic Mechanisms

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Background: Human emotional phenotypes are controlled by both genetics and environment. Experience, particularly during sensitive periods early in life, leaves indelible marks on an individual's resilience or vulnerability to stress-related emotional disorders. There is evidence that early-life experiences influence the function of brain neurons involved in these crucial behaviors by modifying neuronal gene expression via epigenetic processes. However, it is not known how early-life experiences signal to specific brain cell populations and how these signals influence the orchestrated programs of gene expression that mediate phenotypic resilience or vulnerability.
Methods: Here we capitalized on observations that a resilience-promoting early-life experience–augmented maternal care—reduces the numbers and function of glutamatergic synapses onto stress-sensitive hypothalamic neurons and represses expression of the stress-sensitive gene, CRH (Korosi et al., 2010). In hypothalamus in vitro, we found that reduction of glutamatergic receptor activation sufficed to recapitulate the effects of augmented maternal care on CRH repression. This effect required enhanced expression and recruitment of the transcriptional repressor REST/NRSF to the CRH gene. NRSF binding was accompanied by epigenetic changes to histones and DNA in immature and adult rats experiencing augmented maternal care. NRSF ChIP-seq analyses identified the gene networks that, in addition to CRH, contribute to the phenotypic changes initiated by the neonatal experience.
Results: In hypothalamus in vitro, we found that reduction of glutamatergic receptor activation sufficed to recapitulate the effects of augmented maternal care on CRH repression. This effect required enhanced expression and recruitment of the transcriptional repressor REST/NRSF to the CRH gene. NRSF binding was accompanied by epigenetic changes to histones and DNA in immature and adult rats experiencing augmented maternal care. NRSF ChIP-seq analyses identified the gene networks that, in addition to CRH, contribute to the phenotypic changes initiated by the neonatal experience.
Conclusions: The current studies are the first to causally connect neonatal environmental sensory experiences, synaptic modulation and epigenetic processes within select neuronal populations. They provide a novel mechanistic pathway from early-life experience to phenotypic outcomes that govern human health and disease.
Keywords: Epigenetic, resilience, Neuroplasticity, stress, Neuronal Epigenome
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