“The impact of prenatal stress and neonatal handling on neuronal development in the limbic system”

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ABSTRACT

The way in which experience sculpts developing neural circuitry is one of the most intriguing questions in developmental neurobiolgy. Evidence has been accumulating that epigenetic factors affect the development of brain and behavior in a much more pronounced way than previously appreciated. However, the cellular mechanism of such experience-driven developmental changes are far from being understood. The present study provides the first evidence that stress *in utero* represents an epigenetic factor which can considerably interfere with the development of neuronal morphology in the rodent limbic system.

In recent years, the role of psychobiology in understanding abnormal behaviors has become increasingly important. There has been increased awareness that various forms of pathological behavior in humans might be the outcome of adverse or traumatic experiences such as stress, occuring early in life. For instance, stress experienced by a mother during pregnancy have been shown to act as a predisposing risk factor in the development of schizophrenia, depression, autism, Hyperactivity-attention-deficit-disorders in the offspring. Similarily, there is considerable evidence indicating that the separation of infant from the mother during the first weeks of their life may lead to behavioral problems at adulthood. Our working hypothesis postulates that exposure to stress during critical developmental periods interferes with the development of neuronal morphology and the establishment and refinement of synaptic circuits. Based on our hypothesis the aim of my study was to identify the impact of prenatal stress and neonatal handling on the development of neurons and their synaptic networks in the rodent limbic system. Limbic system is a target for hormones involved in stress response and has been implicated in several behavioral and psychiatric disorders that are exacerbated or precipitated by stress exposure. Thus, assessment of the effects of stress on the limbic

system may have important implications for the causes and prevention of disorders caused due to dysfunctional limbic system.

Quantitative analysis revealed pronounced changes in the dendritic morphology of pyramidal and granular neurons in response to prenatal stress. Exposure to prenatal stress resulted in significantly lower spine density in the orbitofrontal and anterior cingulate cortices relative to untreated control animals. In addition, there was a significant reduction in the total dendritic length and arborization in the orbitofrontal and anterior cingulate cortices of males, CA3 and CA1 hippocampal areas of both sexes as well as in the basolateral nucleus of males. Present study also provides evidence that the effect of prenatal stress is sexually-dimorphic. The neuronal morphology of males and females are altered differentially by prenatal stress. This study further indicated that the neuronal alterations induced by prenatal stress are prevented or reversed by neonatal handling. Neonatal handling prevented stress-induced neuronal alterations in a sex, region and dendritic-specific manner. Present study also demonstrated that the separation of infants from the mother during the early weeks of life caused significant alterations in the spine density and dendritic morphology of pyramidal and granular neurons which markedly differs between the sexes. Finally, this study revealed that there is considerable sex-differences in the neuronal morphology of untreated control animals. The spine density and dendritic morphology of pyramidal and granular neurons are organised differently in the brains of untreated male and female rats. The findings of this study provides a neuroanatomical substrate for the behavioral deficits described in prenatally stressed and handled animals. Stress-induced morphological alterations might underlie or contribute to the behavioral impairments caused due to stress.