

RESEARCH SUMMARY

Early Life Stress Inhibits Expression of a Novel Innate Immune Pathway in the Developing Hippocampus.

Wei, L., Simen, A., Mane, S. & Kaffman, A.
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Child abuse, or neglect, is endemic in Western societies. In the USA 1.5 million children are affected each year. Maltreated children often suffer a range of behavioural and emotional problems, many of which are unresponsive to treatment. It has been estimated that childhood maltreatment results in one third of adult and one half of child psychopathologies. The cost of this to the US health budget is about \$247 billion per year. To put that cost into context, it is equal to the cost associated with treating all cancers in the USA.

Child abuse and neglect cause early life stress. The neurobiology of this stress is becoming understood. Under stress, the body releases the stress hormone corticosterone. In prolonged stress in infancy, corticosterone restricts the growth of neural connections in the brain. The question is: how are these changes achieved? Invasive experiments on children cannot be carried out. So scientists have to resort to developing animal systems, using mice, where controlled acute maternal separation studies can be performed on new born offspring. Plasma corticosterone levels can be measured in animals without maternal separation (controls) and compared with those subjected to maternal separation. In a similar experimental paradigm, gene expression within the infant mouse brain can then be analysed using whole genome microarray techniques (a grid system where each grid contains a particular gene, and it is possible to read off how much of a particular gene is being expressed from a tissue sample). This method identifies which genes are being expressed during separation treatment. The area of the brain chosen for study was the hippocampus. This region has frequently been implicated in postnatal development affected by maternal care.

From the results with microarray analysis of gene expression, it became clear that in the developing hippocampus, there was a decreased expression (down regulation) of a lipopolysaccharide binding protein (LBP) in the offspring associated with maternal separation. LBP is a protein involved in the immune system; in the hippocampus it is regulated by corticosterone levels, possibly through the LBP promoter glucocorticoid binding site. Genetically modified mice without the gene for LBP (knockout mice) show behavioural abnormalities that resemble mice with early life stress.

In summary, a key protein involved in the immune system and the development of the hippocampus is down regulated by early life stress in animal models. This work paves the way for a more detailed understanding of stress pathways in children who are neglected or abused.

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