**RESEARCH SUMMARY**

**The pathways from mother's love to baby's future**

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For all of us, what we experience in early childhood (and particularly as babies) influences how we will respond to stress throughout our lives. The quality of the developing relationship between an infant and its mother has been seen to be especially important in determining that infant's subsequent reactions to stressful situations and thus the adult's mental health. These observations formed the basis of Bowlby's theory of social attachment, which states that interactions between mother and baby, whether loving or neglectful, act to "program" the baby's developing brain and fix the way the individual instinctively responds to stress in later life. Therefore, excellent, loving maternal care in babyhood can confer some resilience to, for example, mood disorders such as depression in later life. Conversely, babies who are neglected or abused by their mothers will grow into adults who are more susceptible to this type of illness. The most extreme cases of this were seen in children who spent their early years in institutions and who suffered from developmental problems that could be cured at least partially if they were transferred to loving foster families.

Scientists now understand quite a lot about the mechanisms that drive this relationship between early life experiences and emotional health in later childhood and adulthood. In both humans and animal models, the quality and quantity of early maternal care triggers long-term changes in the ways in which various genes associated with the stress response are expressed. This means that different types of care will cause differences in the amounts of the proteins derived from these genes, and therefore differences in brain biochemistry that affect both mood and behaviour. However, there are still many unanswered questions about both the mechanisms and the consequences of this genetic response. Aniko Korosi and Tallie Baram from the University of California at Irvine, California, USA have written a wide-ranging review of the research literature on this topic in an attempt to answer some of these.

There are many practical and ethical reasons why it is much easier to conduct studies of the influence of early-life maternal care on development using animal models than using human subjects. Korosi and Baram described research in rats starting over half a century ago that showed that the hypothalamic–pituitary– adrenal (HPA) system in the brain was involved in the hormonal (cortisol) response to stress and that this could be affected by the quality and quantity of interactions between a mother rat and her pups. Researchers have shown that pups reared by mothers who naturally exhibit enhanced nurturing behaviour (licking and grooming) show a reduced hormonal response to stress when mature. Similar results were obtained from experiments designed to artificially enhance or reduce the quality or quantity of the care offered by the mother rats. Lower levels of a peptide stress hormone, corticotropin releasing

factor (CRH), and higher levels of the glucocorticoid receptor (GR) were found in the brains of adult rats that had experienced higher-quality care as pups. This receptor binds to the stress hormone cortisol and similar molecules, removing them from circulation. The effect of these biochemical changes is likely to be to dampen the natural stress response and to improve learning and memory. Conversely, rat pups separated from their mothers for long periods soon after birth exhibited raised levels of circulating stress hormones and more fearful behaviour. Similar responses were seen in pups raised by mothers that had been deprived of nesting material, a situation that is expected to lead to erratic, fragmented maternal care. These hormonal changes persisted through the lifetime of the adult rats.

Many researchers have explored the molecular mechanisms that might lead from alterations in maternal care to long-lasting changes in hormone levels and stress responses in rodents. The expression of a gene as a functional protein is mediated through a third molecule, known as messenger RNA (mRNA), which is produced directly from the gene sequence. Levels of mRNA produced from stress-related genes in the brain are known to be altered by interactions between a pup and its mother, and these alterations differ in different brain regions and in time. As an example, Korosi and Baram described what is known about the sequence of molecular changes that occur in the brain of an infant rat as a result of artificially enhanced maternal care. Several independent experiments have shown that the first such change to occur is a decrease in the levels of mRNA produced from the gene for the hormone CRH, implicating the production of this hormone as a key step in building stress resistance. This occurs largely in a specific region of the hypothalamus of the brain known as the paraventricular nucleus (PVN). It seems likely that individuals with genetic differences in this hormone, or in receptors that lead to lower levels of circulating hormones, will similarly be resistant to stress.

If, as seems very likely, similar molecular mechanisms occur in other mammals including humans, it will be important for us to learn how signals from the mother's care can pass into neurons in the PVN to trigger this response. Neurons in the PVN that express the hormone CRH are known to be the targets of a cascade of many biochemical signals that are triggered by earlier chemical changes to other proteins. In particular, the gene for CRH can be activated by the addition of phosphate groups to two proteins farther back in the biochemical cascade. These proteins, CREB and ERK, are transcription factors – proteins that influence gene expression and thus the production of other proteins – and a removal of phosphate from these molecules will lead to a reduction in CRH levels that can last throughout the lifespan of the rat.

The research reviewed by Korosi and Baram therefore suggests that control of the production of the peptide hormone CRH is both an early and a key step in the pathway that leads from maternal care of an infant to the inbuilt stress responses of the adult. It is likely that this pathway, extensively researched in rodent models, is replicated in humans. If so, it should be possible to develop drugs that block the production of this hormone or its activity at its receptors, and thus compensate to some extent for the emotional and developmental disadvantages incurred by disruption to the crucial bond between a human baby and his or her mother.

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