

# Neuro-endocrinology

## BRIEFINGS

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### SUMMARY

How does “nurture” change the brain? Recent evidence suggests that maternal care may shape the infant brain by turning genes “on” or “off” during development. Some of the genes affected are important for maternal and social behaviour leading to long-term changes in the nurturing behaviour of offspring. These studies provide new insights into the inheritance of behaviour and the interactions between genes and the social environment across the lifespan.

*Studies of maternal behaviour in the rat suggest that mothering is transmitted epigenetically from mother to daughter through levels of methylation of the ER $\alpha$  gene promoter.*

## NURTURING NATURE: SOCIAL EXPERIENCES AND THE BRAIN

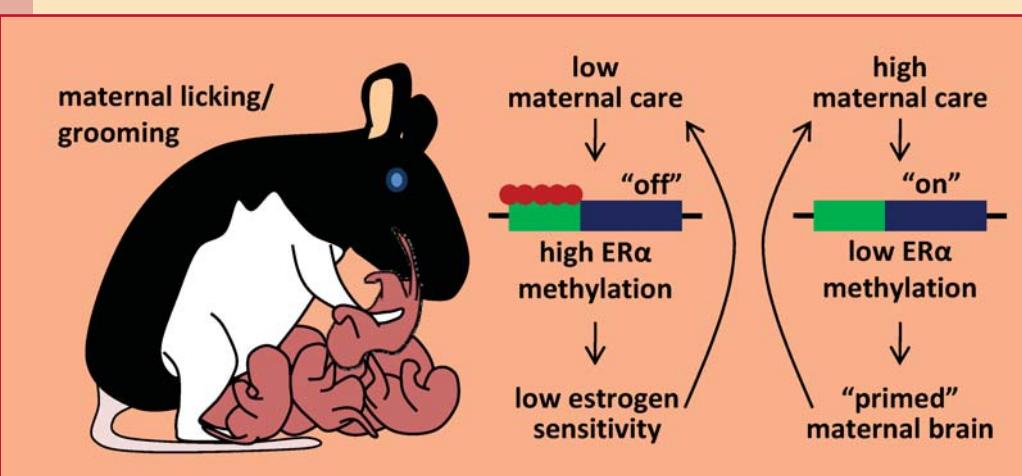
### Maternal care

Early in life the infant brain is rapidly changing, making this a very sensitive time during which experiences that can alter the central nervous system may have an enduring effect. To explore how the brain is shaped by these experiences, studies have been conducted on the neurodevelopment of rodent pups who receive either low or high levels of maternal care. Newborn rodent pups, like human infants, need to be fed, kept warm and stimulated in order to grow. Rodent mothers provide this stimulation by licking and grooming (LG) their pups. However, not all mothers provide the same level of care toward their offspring. Individuals who receive low levels of LG are found to have fewer glucocorticoid receptors within the hippocampus as well as altered dopamine, serotonin and GABA neurochemical pathways in the brain. These neural changes

emerge early in infancy and are sustained into adulthood with consequences for behaviour across the lifespan.

### Like mother, like grand-daughter

In both humans and animals, there is evidence that mothers and daughters are very similar in their styles of maternal care. This is most certainly true in rodents, as those mothers who provide low levels of LG tend to have offspring who also engage less frequently in this form of maternal care. Though one might suggest that this transmission of maternal care over generations could be due to genetic variation that is passed from mother to daughter, cross-fostering studies have shown that it is the quality of care received in infancy that predicts offspring maternal behaviour. Moreover, these effects can be passed on to subsequent



generations of female offspring, such that mothers, daughters and granddaughters are similar in their patterns of maternal care. To understand how this generational transmission of behaviour occurs we must first understand what mechanisms in the brain can drive individual differences in maternal behaviour.

## Primetime

Late in pregnancy, levels of estrogen rise dramatically in order to increase oxytocin receptors (OTR) in the uterus, mammary gland and hypothalamus. This up-regulation of receptors is of critical importance in priming the female for the process of giving birth, lactating and forming an attachment with the newborn. In order for estrogen to alter levels of OTR, this hormone must bind to estrogen receptors (ER $\alpha$ ) which are located within the cell nucleus. The estrogen/ER $\alpha$  complex can then bind to the promotor region of the OTR gene and increase the level of transcription. Low LG mothers have reduced levels of OTR and ER $\alpha$  in the medial preoptic area of the hypothalamus. These neuroendocrine systems are similarly altered in the offspring of low LG mothers, with the result of altering the sensitivity of these females to hormones in late pregnancy. Thus, maternal care received can alter whether a female's brain will respond to hormonal priming of maternal behaviour, leading to the transgenerational transmission of these maternal effects.

## Gene switches

The critical pathway that allows for the "inheritance" of maternal care involves stable increases in the activity of the ER $\alpha$  gene. This raises the intriguing question of how changes

*"....the quality of mother-infant interactions can serve as an "on/off" switch to gene expression..."*

to a gene's activity can persist long after the experience of maternal care. Levels of gene expression are ultimately determined by how accessible the sequence of DNA is to factors which initiate the process of transcription. However, these factors can be blocked by a very stable and heritable chemical modification known as DNA methylation. When DNA is methylated it is no longer accessible to transcription factors and gene expression is thus "silenced". DNA methylation is referred to as "epigenetic" because this modification alters the activity of genes without altering the sequence of their DNA. Recent studies have shown that the experience of low levels of maternal care in infancy can lead to increased levels of DNA methylation within the promotor region of the ER $\alpha$  gene leading to reduced levels of receptors in adulthood. Thus, the quality of mother-infant interactions can serve as an "on/off" switch to gene expression with consequences for neurobiology and behaviour.

## Across the lifespan

While the brain is likely to be particularly sensitive to experiences occurring early in development, there is a high degree of plasticity in the brain beyond infancy. Maternal and social behaviours can be influenced by the quality of the juvenile environment and prolonged exposure to stress is effective at shifting patterns of behaviour across the lifespan. In rodents, juveniles who are placed in a

socially enriched environment are later observed to exhibit high levels of hypothalamic OTRs and maternal care whereas when juveniles are socially isolated, or adult females are stressed during pregnancy, they are found to have fewer OTRs and decreased maternal care. Though it is not yet known how these changes occur, it is possible that these environmental experiences turn genes "on" or "off" through epigenetic pathways. In gaining a better understanding of how the environment can shape gene expression and the brain we may be able to develop new strategies for intervention in humans to reverse the effects of early life adversity.

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