RESEARCH SUMMARY

Intergenerational Transmission of Stress in Humans

Bowers, M.E. and Yehuda, R.

Neuropsychopharmacology REVIEWS (2016) 41, 232-244

It has been known for many decades that severe exposure to stress in a parent is a risk factor for problems including, sometimes, psychiatric disorders in their offspring. Several mechanisms have been suggested for this: these include the inheritance of genetic risk factors for vulnerability to stress, the effect of stress on parenting ability, and, in recent years, that chemical changes to the genetic material (the DNA) of the parents that arise from stressful experiences can be passed on to the offspring. This biological transmission of stress-related problems between generations has come to be known as the intergenerational transmission of stress. It is the subject of a recent review in *Neuropsychopharmacology REVIEWS* by Mallory Bowers and Rachel Yehuda of Icahn School of Medicine at Mount Sinai, New York, USA.

Bowers and Yehuda began by clarifying the topic of their review further, distinguishing between the effects of past parental stress on children – intergenerational transmission – and the direct transmission of psychiatric difficulties from parent to child through observation and learning. Furthermore, the review has been restricted to discussing studies in humans; similar results obtained using other mammalian species are mentioned only briefly and as comparisons. It does, however, aim to distinguish between the effects of parental stress on the offspring from those of parental psychiatric disorders.

Stress theory as developed by Hans Selye in the 1950s states that a physiological response to a challenging environment is common to all organisms. When that challenge is short-lived, the removal of the stress triggers a return to a 'normal' state. Long-term stress, however, can cause lasting physiological changes. The establishment of post-traumatic stress disorder (PTSD) as a formal diagnosis in 1980 highlighted the problem of the adverse effects of prolonged stress and probably started the serious scientific study of long-term stress responses. At the same time, advances in molecular biology and neuroscience have helped develop our understanding of the biochemical nature of this response. Individuals whose parents endured severe trauma have contributed to this research by describing their experiences, and it has become possible to distinguish between effects of stress that are seen in both generations at once and those that occur in the offspring but not the traumatised parents.

Intergenerational transmission of stress, then, is not behaviour that children learn from their parents, or emotions experienced vicariously when children imagine what their parents endured. It is also not a result of the poor parenting that can be caused by current or former stress. It is the intriguing idea that traumatic experiences lead to biological changes in parents that are transmitted directly to their offspring. This mechanism was first suggested in the 1990s from studies of the offspring of women who were pregnant during the Dutch famine in the 1940s. In several cases these middle-aged people were found to be still suffering from deprivation experienced by their mothers before they were born. The results of these, and similar, studies have suggested that stress may be transmitted via the parents' gametes (egg and sperm), the environment inside the uterus during pregnancy, and/or through effects on early postnatal care. Although most studies have concentrated on the effect of the mother, some have indicated that paternal stress can also be transmitted through changes to the

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sperm or to early paternal care. Changes to the genetic material and to the structure and function of the brain in offspring have been found to arise through all these mechanisms.

Many studies have suggested that the children of parents who experienced severe stress, maybe years before they were conceived, are at a high risk of developing stress-related disorders, anxiety or depression. These effects have been seen in adult offspring of Holocaust survivors born after the end of the war, and, much later, in offspring of women who experienced the 9/11 attacks directly during their pregnancies. Severe stress during pregnancy has been associated with low birth weight and premature birth, and these infants are more likely to develop several chronic diseases in adulthood than those born at a healthy weight and at term. Increases in these diseases have also been observed in the adult offspring of Holocaust survivors.

Children of mothers stressed during pregnancy and children of Holocaust survivors have also been found to be of greater risk of mental and emotional difficulties than those whose parents experienced no severe stress. Studies of mothers stressed during pregnancy have shown an association between maternal anxiety in the second and third trimesters and behavioural and emotional problems in their children. Maternal anxiety also seems to affect the cognitive function of their offspring, particularly in areas related to concentration and memory. And these emotional and – probably – cognitive difficulties may explain why the offspring of traumatised parents are more vulnerable to psychiatric problems later in life. One study found that the offspring of Holocaust survivors were more likely than others of the same age to develop PTSD after military service; comparable results have been seen in individuals whose mothers experienced (for example) a natural disaster during pregnancy.

Bowers and Yehuda went on to consider some potential difficulties with the methodology of studies of intergenerational stress transmission in human subjects. There is often a difficulty in deciding whether measured effects in offspring are determined more by the severity of the stress endured by the parents or by that of the symptoms they suffer: that is, by parental biology or parental behaviour. One paper in the *Lancet* describing the impact of an ice storm in Quebec in 1998 on the offspring of women caught up in it sought to distinguish between ‘objective’ stress (the extent of the mothers’ exposure to the storm) and ‘subjective’ stress (the severity of their PTSD-like symptoms). Furthermore, unless the participants have experienced a single, over-arching stressful event (such as 9/11) it is difficult to determine exactly when stress transmission will have taken place. Studies of interactions between parents, children and their environment are also quite limited, and the transmission of stress from the father – which seems to be less marked than that from the mother, but is undoubtedly a problem – has not been widely studied. One study of the offspring of Holocaust survivors has suggested that paternal PTSD has no direct effect on the children but can make the effect of maternal PTSD worse. Studies with larger numbers of subjects, more detailed participant histories and comparison with experiments in animal models should all help clarify the outcomes of these complex experiments.

Next, Bowers and Yehuda reviewed studies of the biological mechanisms through which stress can be transmitted between generations. These mechanisms are extremely complex, and they are certainly not yet fully understood. They can, however, be grouped into three broad categories, relating to hormonal changes, epigenetic changes to DNA and changes to the brain anatomy.

The most widely researched of these areas is the hormonal one, and in particular the relationship between three hormone-releasing glands: the hypothalamus and the pituitary in the brain, and the adrenal glands above the kidneys. This so-called ‘HPA axis’ controls the synthesis (manufacture) of the ‘stress hormone’, cortisol, and its release from the adrenal

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glands. Both the times of day at which cortisol is released, and the total amount released, are affected by stress, and abnormal cortisol patterns have been correlated with untypical stress responses. The activation of the HPA axis and release of cortisol is part of the normal stress response, helping to prepare the body for an expected 'fight or flight' response: abnormal patterns only occur when stress is prolonged. Post-traumatic stress disorder is thought to arise when the HPA response is cut short prematurely, and people with this disorder have cortisol levels that are lower than normal. Cortisol circulating in the body is able to reach the gametes and the developing foetus. Children who have a parent – particularly a mother – who suffers from PTSD have also been found to have low cortisol levels as well as being at risk from PTSD themselves. This effect is found to some extent in children of Holocaust survivors, regardless of whether the parents have observable ill effects.

Studies of stress-related conditions other than PTSD have also shown changes to HPA activity and cortisol response in offspring, although the pattern is rather more complex. Several studies have shown correlations between anxiety during pregnancy and changes to the daily pattern of cortisol release in children and adolescents of different ages. One found that the 14-year-old offspring of women affected by the Chernobyl disaster during pregnancy had significantly higher cortisol levels than adolescents whose mothers had not been exposed to the stress of this incident. Differences between studies in this area may be related to differences in the gestational age at which the mothers were exposed to stress; the age of the children or young people involved; and the method of measuring stress.

Other researchers in this area have looked at the relationship between cortisol levels in pregnant women (as a proxy for exposure of the foetus in utero), in amniotic fluid, and in infants. High levels of cortisol have been observed in the blood of infants, pre-school and school-age children of mothers who recorded high cortisol levels during pregnancy; however, none of these studies so far have looked at the relationship between maternal cortisol levels and stress. There is much work still to be done; for example, no studies have yet linked parental stress to offspring behaviour via cortisol levels, and little is known about the involvement of enzymes in the placenta in regulating the amount of cortisol that reaches the foetus.

Studies of epigenetic mechanisms for the transmission of stress between generations have largely focused on chemical changes that affect a gene called NR3C1. This gene is also involved in the body's response to cortisol: its expression causes the synthesis of a protein called the glucocorticoid receptor (GR), which binds to and is stimulated by cortisol. The addition of small chemical groups to part of the DNA that makes up this or any gene (in a process called methylation) typically inhibits the synthesis (or manufacture) of the associated protein. These changes can persist for many years and be passed between generations; changes to NR3C1 methylation have been observed in the offspring of both Holocaust survivors and mothers who were stressed during pregnancy. However, results from all studies in this area are not completely consistent: pre- and perinatal stress was associated with NR3C1 methylation in the adolescent offspring of mothers who were pregnant during the Rwandan genocide in 1994, but not in the offspring of some other stressed groups. Larger studies over longer periods of time will be needed to determine the overall pattern of NR3C1 methylation in offspring due to parental stress and its association with emotion and behaviour.

Some epigenetic studies have focused on the gene for the serotonin transporter, which is known as SLC6A4. The serotonin transporter is the target for anti-depressant drugs such as Prozac, which increase the concentration of serotonin by blocking its transport. Stress in pregnancy has been associated with methylation and decreased expression of this gene and therefore with lower serotonin transporter levels. Interestingly, some people carry a mutation in this gene that leads naturally to decreased serotonin transporter levels, and the lowest

levels of the protein have been found in individuals with this mutation whose mothers had also been stressed. Changes in the expression patterns of genes linked to depression and to the immune system have also been linked to maternal stress, although these studies are all in early stages.

Other researchers have examined the relationship between parental stress and brain development in the offspring. These have primarily focused on brain regions known to be associated with emotional development and the stress response, including the frontal cortex and the hippocampus. It is thought that changes in the anatomy of these regions that have been observed in some studies of the children of stressed mothers may be associated with changes to the brain pathways that process emotion. Similar changes have been observed in children whose mothers took synthetic glucocorticoids – drugs with similar structures to the natural hormone cortisol – during pregnancy.

Bowers and Yehuda conclude their comprehensive review by setting out some suggestions for future directions of research. They suggest that comparisons between adoptive and biological parents might be useful in confirming the role of the pre-birth environment in stress transmission. They also highlight the persistence of the stress response in subsequent generations as a rewarding research area, commenting on a study that suggests that stress has been transmitted to the grandchildren of Holocaust survivors.

One further topic highlighted for further research was the nature of factors that might block the development of stress-related problems in the children of stressed parents. Recent work has suggested that infants brought up in stable, nurturing relationships may indeed be protected from at least some of the effects of parental stress. While much in this field is still unknown, the importance of such a secure environment in mitigating stress is a clear ‘take-home’ message from this wide-ranging review.

Dr C. Sansom

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