Nature and Nurture? The intergenerational transmission of risk for chronic illness

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Glossary

While it is not strictly necessary to know all of the terms used in this summary, readers may find it useful to have a definition of key terminology.

Neural: Referring to the nervous system, a network of cells which specialise in co-ordinating actions and passing signals from one part of the body to another.

Endocrine system: A group of glands which secrete hormones which regulate the body's internal state.

Epigenetic: Any functional change in the genome that does not involve an alteration of DNA sequence e.g. structure or level of activity.

Glucocorticoid: A class of steroid hormones the active presence of which reflects a response to stress or the circadian rhythm.

Glucocorticoid receptors: Proteins responsible for sensing the presence of glucocorticoids, regulating genes which control development, metabolism and stress responses.

Hypothalamus: A small part of the brain which, among other functions, links the endocrine system to the nervous system through the pituitary gland and is therefore important in stress responses.

Corticotrophin-releasing factor (CRF): A hormone released by the hypothalamus in response to stress, which in turn activates multiple features of the stress response, including the release of glucocorticoids throughout the body as well as noradrenaline in the brain.

Adrenal Glands: Glands which are situated just above the kidneys in mammals and are chiefly responsible for the release of stress hormones, including the glucocorticoids.

Hypothalamic Pituitary Adrenal Axis (HPA): A system that includes hypothalamus, the pituitary gland and the adrenal glands, which control reactions to stress and regulates many body functions including the processing of fats and glucose.

T3: An abbreviation for tri-iodothyronine the most powerful thyroid hormone affecting almost every body process including body temperature, growth and heart rate.

Metabolic Rate: The amount of energy required for the functioning vital organs: illness, environmental factors and stress levels affect metabolic rate.

Transcription factor: A protein which binds to specific DNA sequences and thereby controls the transcription and activation of information from DNA.

Neural Growth Factor Inducible (NGFI-A): A specific transcription factor, which binds to the part the genome sequence, which produces the glucocorticoid receptor, associated with stress response. When activated by maternal stimulation at high levels it displaces a methyl group and allows the glucocorticoid receptor to be read, thus more effectively regulating stress response.

Cytosine: One of the four basic building blocks (nucleotides) of DNA.

DNA methylation: This involves the addition of a methyl group (CH_3) to a cytosine on a DNA sequence. This commonly has the effect of blocking or reducing gene expression. In the case of stress, it prevents the activation of Glucocorticoid receptors which are needed for an appropriate response to stress.

Overview

In this lecture Professor Meaney showed that the development of an individual in almost any species is a process of adaptation that occurs within a social and economic context. Referring to studies in various species, he showed that the effects of social and economic circumstances (resources) are mediated through parental, particularly maternal, behaviour and that this behaviour interacts with gene structure and activity to alter stress response into adulthood.

Summary

Professor Meaney began by reminding us that many studies show a link between early experience in childhood and later onset of chronic illness such as obesity, depression, heart disease and diabetes. A key issue here concerns the mechanisms by which vulnerability or resilience is transmitted from parent to offspring.

He asked what mechanisms in early life experience cause such transmission. One such mechanism is the transmission of genetic variation from biological parents. However, recent studies reveal other processes which focus on the interaction between parent, particularly mother, and offspring. He suggested that in a wide range of species, including humans, maternal care alters the development of behavioural and endocrine responses to stress. These 'maternal' effects are due to stable changes in the expression of genes in brain regions that regulate stress responses.

He suggested that early life experiences including environmental adversities like poverty are, in part, mediated by parental factors and that these are related to differences in individual neural and endocrine responses. He illustrated this point from a study[1] which showed poverty impacted upon maternal stress, which in turn affects parenting and then shows up in child behavioural and emotional problems. He summarised his argument at this stage by saying that early life experience interacts with individual differences in neural and endocrine responses, which is reflected in different stress responses. These patterns of individual differences in stress response tend to last into adulthood. The question is how? What sustains these maternally-influenced individual differences?

One can see similar biological responses to environmental stress across species. For example he showed how skink lizards (a source of food for snakes) grow larger, and with longer tails when born after their mothers have been exposed to predatory snake scent.

Similarly, water flea larvae of the same genotype grow a helmet and a tail, making them more difficult to ingest after exposure to water previously containing predators. This physical defense is passed on to their offspring. He suggested that this type of stress response is common across almost all species of mammals, reptiles and plants and is not limited only to humans.

These simple examples show that the quality of the mother's environment influences the development of her offspring and this and other examples suggest that this theme (environment – parent – offspring development) is common in biology.

[1] Linver, M.R., Brooks-Gunn, J. and Kohen, D. (1999) 'Parenting behaviour and emotional health as mediators of family poverty effects upon young low-birth weight children's cognitive ability', *Annals of the New York Academy of Sciences*, 896( ), pp376-378

What is the connection between the social and biological dimensions of stress and stress response?

Professor Meaney summarised this part of the argument thus:

- Parental care affects the activity of the offspring's genes in the part of the brain that regulates stress responses, neural development and reproduction.

- This parental effect involves a form of "plasticity" at the level of the DNA. While the gene sequence remains unchanged, gene structure and activity are altered. This allows for the production of more Glucocorticoid receptors which help to prevent a heightened stress response

Drawing upon knowledge of rat populations he highlighted the importance of maternal licking/grooming of offspring. He showed that offspring which are licked extensively during the first ten days of life have an increased number of Glucocorticoid receptors on a specific part of the regulatory portion of their gene sequence (i.e. the region of the DNA that determines the activity of the glucocorticoid receptor gene). The activation of the glucocorticoid receptor protein in a brain region known as the hippocampus restrains the magnitude of the stress response.

This has the effect, in stressful situations, of preventing a heightened response to stress. This in turn has beneficial effects on other systems vital for health, for example, the cardiovascular system, obesity and depression, through its impact on metabolic rate and the activation of noradrenaline in the brain. Thus while one's inherited DNA defines the genotype, there are other environment related processes, known as epigenetic effects, which are chemical in nature and are superimposed on the gene sequence (which remains unchanged) but modify the level of its activity.

The mechanism through which this happens is as follows:

- Variations in maternal care (more licking, less licking) modify gene activity and this alters the number of glucocorticoid receptors. This helps shape stress response.

This pattern is shaped in early life and persists into adulthood because:

- This tactile activity associated with the mother's licking stimulates the production of the transcription factor, NGFI-A, which acts to dislodge a methyl group from the cytosine. This allows the same NGFI-A to bind to the cytosine in the regulatory region of the glucocorticoid receptor gene and to activate the production of Glucocorticoid receptors (GCRs).

- This increase in active GCRs mediates the production of stress hormones and helps prevent a heightened response to stress associated with many chronic illnesses.

One might ask if this is really an environmental/behavioural effect or is the DNA of high licking mothers simply different from that of low licking mothers. Adoption studies in which the offspring of low licking mothers are fostered by high licking mothers exhibits the same mediation of stress response and indicates that the effect does come from maternal behaviour. This process also affects the maternal behaviour of the offspring in that the offspring of high licking mothers become high licking themselves. In this sense, the individual differences could be transmitted across generations through a "behavioural" form of inheritance that includes effects at the level of the DNA.

Professor Meaney ended by highlighting a study using human brain tissue comparing suicide victims with those of others who were healthy, but had also died suddenly.

He showed that the brain tissue of suicide victims had lower numbers of glucocorticoid receptors (heightened level of response to stress) compared to the brain tissues of those who had died suddenly from other causes. This is a similar pattern existed to that described above for rats.

A further subdivision of the suicide group – into those abused as children and those not abused – showed that the abuse group had a lower number of glucocorticoid receptors than those with no record of abuse in childhood. The cells also showed higher levels of methylation in the abused group, indicating that the GCR's transcription factors were switched off preventing the cell from mediating stress hormones effectively.

Taken together, these studies suggest that the behaviour of the parent (affected by circumstance and the previous generation) activates a series of intercellular signalling pathways which alter epigenetic marks at specific sites on a genome. This contributes to the transmission differences in individuals across generations.

In conclusion he suggested the key messages from his lecture were:

Firstly, adverse circumstances have an effect on the quality of maternal care in rats. This is manifest in lower levels of licking/grooming in stressed groups and has the effect of preventing the HGFI-A transcription factor from binding to the appropriate cytosine in the gene, preventing the offspring from creating GCRs, which in turn heightens stress response.

This effect can persist into adulthood because high licking (good maternal care) removes methyl cells from the cytosine, opening it up to the effects of NGFI-A which induces the production of GCRs which help mediate stress response. It is this removal of Methyl cells which shapes the ability of the gene to respond well to stress. The effect is reversed for low licking mothers. The effect can be reversed in adoption studies when the offspring of low licking mothers are adopted by high licking mothers.

Secondly, similar effects can be observed and found in other species including human beings, highlighting further the importance of early life experience.