Neuro-endocrinology
13 BRIEFINGS

EARLY LIFE STRESS CAN PROGRAMME OUR HEALTH

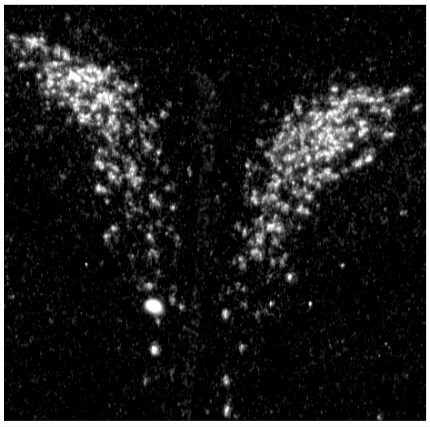
SUMMARY

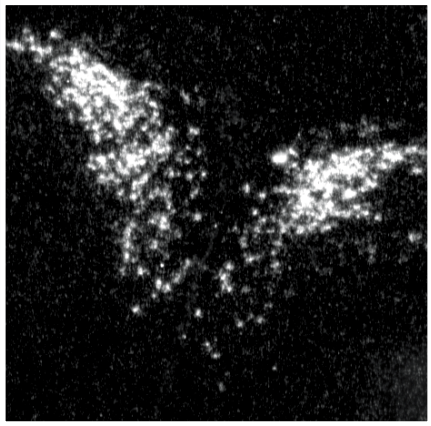
It is essential that the environment for a developing foetus is optimal for normal growth and maturation. Small perturbations in this environment may put that child at risk for developing cardiovascular, metabolic and cognitive deficits later in life. Evidence is accumulating that chronic stress while pregnant may result in lower birthweight babies and a heightened risk of mood disorders and cognitive deficits. Elevated glucocorticoid hormones, induced in the mother in response to the stress, appear to be mediators of events "programming" the developing central nervous system of the foetus and rendering it susceptible to dysfunction in later life.

Nature and nurture

It is clear that the genes inherited from the parents play a major role in determining a child's susceptibility to disease in later life. However, there is increasing evidence that the early life environment also plays a critical role. We all know of the effects of drug and alcohol abuse during pregnancy, but do more subtle environmental changes also affect the foetus?

Several epidemiological studies have shown a correlation of low birthweight, thin babies with a risk of hypertension, impaired glucose tolerance/late-onset diabetes, high blood cholesterol and death from coronary heart disease. These observations led to the "foetal origins of adult disease" hypothesis and an attempt to identify events or factors that can modify foetal development and 'programme' the person or animal to be at risk of cardiovascular and metabolic disorders in later life.





Darkfield photomicrographs showing corticotrophin-releasing hormone (CRH) gene expression in the hypothalamus of the brain from adult rats treated prenatally with vehicle control (left) or the synthetic glucocorticoid, dexamethasone (right). CRH expression is increased in animals that received dexamethasone during days 14-20 of pregnancy. This in turn causes increased drive to the pituitary and adrenal glands and elevated plasma corticosterone levels.

Early life events and brain function

Can early life events also programme brain function? The developing nerve cells of the brain are extremely sensitive to their environment, as growth factors, gene transcription factors and steroid hormones alter cell turnover and migration as well as neuronal network formation. Several rodent models have been used to characterize the consequences of manipulation of the prenatal environment, the most common being prenatal stress, where the pregnant mother experiences an unpredictable stressor, such as random light and noise. Prime candidates for a programming factor are glucocorticoid hormones

(cortisol, corticosterone) produced by the adrenal glands.

Circulating glucocorticoids are elevated in the mother in response to stress, and although there is a barrier inhibiting glucocorticoid movement across the placenta (it makes a glucocorticoid metabolising enzyme), this barrier is leaky and can be saturated, hence increased foetal exposure to glucocorticoids may occur. Administration of a synthetic glucocorticoid or an inhibitor of the enzyme barrier also induces programmed effects in the offspring, similar to the prenatal stress paradigms; namely decreased birthweights, hypertension and high blood glucose.

"Prenatal programming has profound effects on the behaviour of the offspring when they grow up"

Coupled with these observations are associated programmed effects in the brain underpinned by hyperactivity of the hypothalamus-pituitary-adrenal (HPA, or stress) axis. Elevated plasma glucocorticoid levels are maintained by alterations in levels of receptors sensing glucocorticoids in several brain areas, the net effect of which is a reduction in the negative feedback action of glucocorticoids to restrain the HPA axis. This is coupled with elevated expression of corticotrophin-releasing hormone in a specialized cluster of nerve cells in the hypothalamus region of the brain which provides increased drive to the pituitary and adrenal glands.

Perhaps, not surprisingly, prenatal programming has profound effects on the behaviour of the offspring when they grow up; they appear more anxious when assessed in elevated maze and open field behavioural tests. Cognitive abilities of the animals are also affected by prenatal programming. Offspring show reduced learning in a discrimination task and reduced learning of spatial memory tasks in a "watermaze". Behavioural changes are correlated with neurochemical changes in the amygdala, an area of the brain mediating fear and anxiety.

Are human babies at risk?

So the brain can be programmed during gestation in rodents, but is this relevant to humans? Strikingly, low birthweight has been identified as a risk factor for autism, depression and suicide. Maternal stress (for example the death of the spouse) during pregnancy is associated with decreased gestation length and decreased foetal growth followed by psychopathology and disturbed behaviour in the children. Furthermore, *postnatal* stress predisposes children to developmental delays, behavioural disturbances and personality disorders later in life. This suggests that the programming window continues past birth into the neonatal period. However, it is difficult to dissociate postnatal maternal care from events in the womb as often the same harmful environmental circumstances will be common to both.

Is there anything we can do?

It is possible, however, that a detrimental experience in the womb can be counteracted by postnatal care. Animal studies using a paradigm of postnatal handling, which stimulates maternal licking and grooming of rodent pups, produces a beneficial programmed effect on the adult's HPA axis activity and behaviour, negating the detrimental effects of prenatal stress. However, it remains true that a proportion of people will be adversely programmed in the uterus and be at risk for cardiovascular problems, metabolic diseases and cognitive dysfunction in later life. For this reason, the medical community should be aware of long term consequences of environmental factors in perinatal life and should intervene where appropriate to reduce any adverse stimuli; for example, counselling could be provided to reduce stress effects of bereavement and other psychological traumas, and unnecessary glucocorticoid administration to pregnant women or newborn children should be avoided. This exciting research drawing links between early life environment and the development of adult disease gives us the potential to look for early risk-factors and then step-in with preventative therapies for those at risk.

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