Neuro-endocrinology
BRIEFINGS
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FETAL EXPERIENCE: LIFELONG CONSEQUENCES

SUMMARY

Modification of the fetal environment has lifelong consequences for endocrine function and behaviour. Maternal stress through activation of the hypothalamus-pituitary-adrenal axis can lead to increased anxiety levels and stress reactivity in offspring. Furthermore, these effects can pass across generations. The race is now on to understand the mechanisms involved and to find ways to prevent or reverse the effects of an 'adverse' early environment in human populations.

In the beginning...

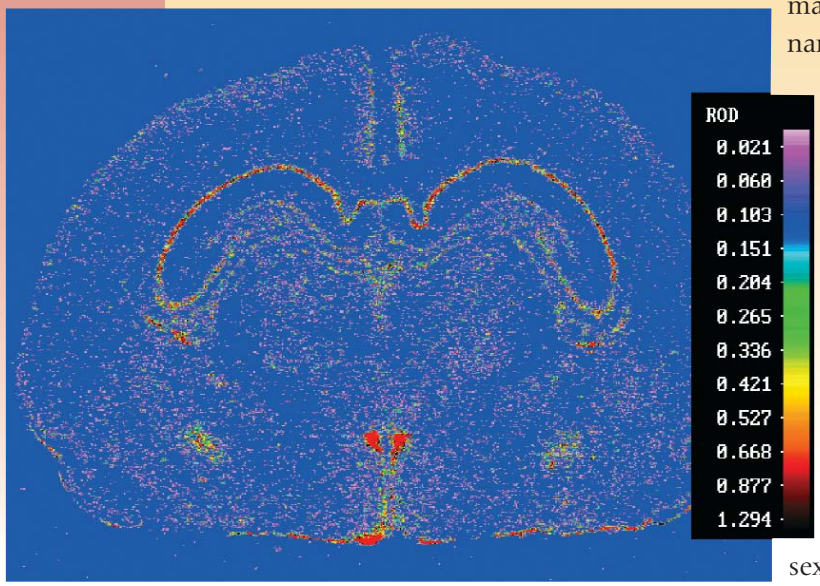
Early life experience profoundly influences endocrine function and behaviour throughout life and into the next generation. This concept has been known for many years; however, the field has been reinvigorated since epidemiological studies correlated low birthweight with increased risk for developing hypertension and diabetes in human populations around the world. These observations have led to the concept of 'developmental origins of health and disease'.

But why do we possess the ability to so effectively 'program' our offspring? It has been suggested that in humans, low birthweight, a surrogate marker of fetal well-being, indicates limited nutrient availability to the fetus, either though inappropriate maternal nutrition or compromised placental function. The fetus adapts its development in anticipation of similar limitations after birth. However, if after birth, food is plentiful, then the individual is maladapted to the environment and at increased risk of developing disease. This phenomenon is even easier to conceptualize in animal populations. If pregnant animals experience a high level of predation pressure, it makes sense to produce offspring that also exhibit heightened anxiety, which will ultimately reduce the risk of being eaten!

Worried mothers

Human studies indicate that increased maternal anxiety during pregnancy results in young children who exhibit attentional disorders and hyperactivity. Similar behaviour patterns have emerged from animal studies, where mechanisms can also be investigated. In several species, maternal stress during pregnancy leads to offspring that exhibit altered behaviours and hypothalamus-pituitary-adrenal (HPA) axis responses to stress.

A limitation of animal studies in this field has been the huge variation in the nature of the experimental manipulations utilized. These include differences in the timing, duration and intensity of the maternal stress, together with the age and sex of offspring. Recent studies



Expression of the glucocorticoid receptor gene in the cornu ammonis (CA) and dentate gyrus (DG) of the hippocampus, and in the amygdala (AMG) and paraventricular nucleus (PVN) of the fetal guinea pig brain.

have shown that the timing of maternal stress is critical both in terms of endocrine function and behaviour. Adult male guinea pigs born to mothers exposed to a short burst of psychological stress at 75% through gestation exhibit heightened anxiety, increased basal HPA function and reduced plasma testosterone levels. In contrast, offspring born to mothers exposed to an identical stress at 90% through gestation, exhibit no differences in anxiety behaviour, basal HPA or gonadal function, but show an increased HPA response to challenge. There are thus time 'windows' when components of the developing brain are highly sensitive to maternal stress; such windows are almost certain to exist in humans.

The signal?

How does maternal stress and anxiety signal developmental changes in the fetus? Maternal stress leads to a plethora of endocrine changes in the mother, many of which could pass directly to the fetus or indirectly affect the fetus by altering placental function. However, a series of elegant studies in rats has provided good evidence that maternal glucocorticoid hormones are critical for programming HPA function in offspring. In most species, maternal plasma glucocorticoid concentrations are some 10-fold higher than in the fetus. While glucocorticoids are required for several aspects of fetal development, too much can inhibit fetal growth leading to reduced birthweight. The fetus is actually protected from maternal glucocorticoids by an inactivating enzyme which is abundantly expressed in the placenta. However, while this inactivation barrier is effective at reducing fetal exposure to active glucocorticoids, maternal stress which increases maternal HPA activity also increases glucocorticoid hormones within the fetus.

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Preterm labour

Preterm labour currently occurs in ~10% of all pregnancies, though this number is rising. Maternal treatment with synthetic glucocorticoids (sGC) is extremely effective in maturing the fetal lungs and decreasing neonatal mortality and morbidity in infants born preterm and sGC therapy is used very extensively in the management of preterm labour. Indeed, until recently women at risk of preterm labour were treated with repeated doses of sGC (i.e. betamethasone). Unlike endogenous glucocorticoids, sGC are not substrates for the placental inactivating enzyme and sGC can pass to the fetus. While the intended target is the fetal lung, the fetal brain contains extremely high levels of receptors for glucocorticoids, particularly in structures important in the regulation of behaviour and endocrine function. If glucocorticoids provide at least part of the 'programming' signal to the fetus, are there long-term effects?

Studies in animals suggest that there are long-term effects of single and repeated prenatal exposure to sGC on HPA function, learning and activity. Indeed, many of the outcomes identified are similar to those following prenatal stress. There is less information on outcome in humans. A retrospective study of behaviour in children that were exposed to 3 or more courses of sGC in utero has identified hyperactivity and other behavioural disorders. Follow-up of adults that were exposed prenatally to a single course of sGC revealed no overt phenotype, although markers of insulin resistance were identified. While there is clearly short-term benefit of sGC in preterm labour, the long-term consequences, particularly of multiple exposures, must also be considered.

Crossing generations

Is it possible that our grandmother's experiences during pregnancy can influence our endocrine function and behaviour? Recent animal studies have shown that this may indeed be the case. Prenatal exposure to multiple courses of sGC in rats leads to reduced birthweight in the 2nd generation along with modified gene expression in the liver. In the guinea pig, repeated sGC exposure leads to altered activity and low glucocorticoid levels in the 2nd generation. This raises important new questions. Is there inter-generational memory ... and how is it transmitted?

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