

EDITORIAL

Developmental origin of health and diseasePeter W. Nathanielsz¹ and Vasantha Padmanabhan²¹Center for Pregnancy and Newborn Research, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA²University of Michigan, Ann Arbor, MI, USA

Email: nathanielsz@uthscsa.edu

The Journal of Physiology has a long history of publications at the forefront of the field of fetal and placental function. The 1950s was the period of acute studies in anaesthetized animals (Dawes *et al.* 1956). There then followed the introduction of the chronically instrumented fetal sheep preparation by the Cambridge, Oxford and Yale groups whose work was well represented in *The Journal of Physiology*. Many specific areas have been covered by *The Journal*. These include fetal breathing and central nervous system development (Dawes *et al.* 1972), the development of the concept that the fetal adrenal axis plays a central role in the initiation of labour and matures key organs in preparation for the new physiological challenges of post-natal life (Daniels *et al.* 1973). More recently *The Journal* has been a major source of information in the field of developmental programming (Hoet & Hanson, 1999). *The Journal* has published papers that deal with every aspect of this fundamental and important issue from genetic imprinting (Reik *et al.* 2003) to changes in the fetal cardiovascular system in response to hypoxaemia (Giussani *et al.* 1993). It is therefore appropriate that *The Journal of Physiology* supported two symposia at the November 2005 3rd International Congress on the Developmental Origins of Health and Disease (DOHaD) in Toronto, Canada. The congress was based on four themes: exposures, outcomes, mechanisms and interventions. It covered the areas included in the previous congresses while increasing the emphasis on implications of DOHaD for the developing world. Other new perspectives included evolutionary biology, developmental plasticity, influences

of social hierarchy, effects of prematurity, environmental toxins, populations in transition and statistical approaches. Reviews by invited speakers supported by *The Journal of Physiology* are included in this issue.

The first symposium supported by *The Journal of Physiology* focused on the placenta. The symposium was chaired by William Hay. Leslie Myatt and Abigail Fowden presented invited lectures. The placenta plays a fundamental role in fetal development throughout pregnancy. It is a truism that if the placenta does not develop well in early pregnancy and continue to function properly throughout pregnancy, fetal development is impaired. As Abigail Fowden states, a smaller neonate is less likely to survive at birth and is more prone to adult onset, chronic diseases such as hypertension and type II diabetes (Fowden *et al.* 2006). The placenta constitutes the only fetal supply line. Abigail Fowden's review focuses on placenta nutrient transfer capacity and how it is affected by nutrition and glucocorticoid overexposure. Factors affecting nutrient transfer capacity include size and development of appropriate morphology. Many new state of the art techniques, such as computerized stereology, have been extremely useful as have more common molecular techniques to evaluate transporter abundance. The placenta is a highly complex organ with a high metabolic rate. Thus nutrient synthesis and metabolism within the placenta play key roles in the development of the placenta itself in addition to its ability to provide nutrients to the fetus. The placenta is not just a passive conduit since synthesis of hormonal and paracrine regulators such as prostaglandin can affect, and be affected by, nutrient transfer to the fetus. This review also presents an excellent summary of the new and burgeoning field of epigenetic regulation of gene expression focusing on the IGF-II gene system.

William Hay addresses in more detail the theme raised by Abigail Fowden that fetal and placental metabolism are regulated by changes in the maternal environment (Hay, 2006). The focus of his review is on glucose metabolism. Glucose is the principal energy substance of the fetus. Glucose transport, and particularly the function of the Glut 4 transporter system, are discussed in detail. Normal and pathological function in the

fetus and the placenta are addressed in relation to pancreatic and insulin function both during normal growth and in intra-uterine growth restriction (IUGR). He proposes potential areas for introduction of therapeutic measures to decrease unwanted effects of IUGR based on what is known about transplacental transport of nutrients and hormonal regulation by, and of, the placenta.

Leslie Myatt continues the discussion of imprinting of gene function, transporters, nutrient supply and the effects of glucocorticoids, functions that are also discussed by William Hay and Abigail Fowden (Myatt, 2006). His review covers the important and controversial area of the role of varying levels of oxygen exposure in regulating normal and abnormal early placental development and function. One important area in placental development is the key role of placental mitochondria in exposing the placenta to oxidative stress.

The second symposium supported by the *The Journal of Physiology* dealt with endocrine function in mother and fetus. Stephen Matthews who chaired this session provides evidence, referred to by all the reviews that outcomes depend critically on the window of development in which the exposure takes place (Kapoor *et al.* 2006). The central focus of his review is the presentation of the compelling data that show that the fetal hypothalamo-pituitary-adrenal axis plays a central role in developmental programming in response to the many maternal challenges that result in a sub-optimal fetal environment. The temporal profile of expression of the glucocorticoid and mineralocorticoid receptors is compared in different organ systems and may be one of the basic mechanisms that result in windows of vulnerability to glucocorticoids and other challenges mediated via glucocorticoids. This review discusses the emerging evidence that the consequences to the fetus of various challenges are sex specific. There are now several examples of different responses in male and female fetuses and male and female offspring postnatally (Armitage *et al.* 2004). The mechanisms that are responsible for these interesting sex differences are clearly important for an understanding of issues such as autism, which is much

more common in males than females. Also included in the review are comparative studies to show how general principles can be drawn from data in species that range from the rat to human.

The final review, by David Phillips and Alexander Jones, provides insights and firm evidence on the extent to which the systems and mechanisms described in the other reviews can be extrapolated to human development (Phillips & Jones, 2006). Focusing on the hypothalamo-pituitary-adrenal axis and the developing autonomic nervous system, they provide an excellent demonstration of the relevance of the research on animal models that form the basis of the other reviews. Evidence is accumulating that a suboptimal environment during human development may increase stress susceptibility and human behavioural difficulties such as attention deficit hyperactivity disorders. The review by Phillips & Jones helps us understand the strength of these associations and provides a strong rationale

for more work in this important area of human health.

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