Memories of the fetal heart

Laura Bennet and Alistair Jan Gunn
The Liggins Institute, The University of Auckland, Auckland, New Zealand

ONE OF THE MOST PROVOCATIVE recent findings in modern medicine has been the suggestion from Barker and colleagues (1) that problems of late adulthood, such as coronary heart disease, stroke, hypertension, and non-insulin-dependent diabetes, are associated with metabolic compromise and impaired growth in fetal life. Although the precise mechanisms of how adverse events in utero can program adult disease are unclear and some of the associations are likely to be indirect (6), many of these epidemiological data have now been replicated in experimental preparations (12). The current focus on disease, however, is perhaps a little misleading. In other areas of development, the central importance of early experience during defined windows of maturation for subsequent adult development is well known. The seminal work by Hubel and Wiesel (5), for example, demonstrated that correct visual experience is important for normal visual development, just as whiskers are essential for the development of barrelfield neurons in the somatosensory cortex in mice (11). Thus we should not necessarily link fetal programming with disease or abnormality.

Indeed, the current study by Broberg and colleagues (2) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology is a striking demonstration that apparently adverse events in utero may confer beneficial effects later in life. Just 20 days of exposure to fetal anemia in late-gestation fetal sheep, a relatively moderate insult as judged by the lack of effect on fetal and adult weights, was associated with markedly improved cardiac contractile responses to hypoxia in young adulthood, without changes in baseline cardiovascular function. These data strongly suggest that adaptations made by the fetus to a compromised intrauterine environment, which are undoubtedly advantageous to survival, such as increased left ventricular filling (7), are retained well into adult life and remain advantageous during subsequent compromise. Furthermore, because development of the sheep is highly advanced at birth, these results are also likely to have important implications for anemia or chronic hypoxia in the first few weeks of life.

Although the authors previously showed a doubling of maximal coronary artery conductance after the same paradigm (3), there was no associated increase in cardiac angiogenesis to explain these findings, consistent with studies of chronic hypoxia in fetal sheep (8). As the authors suggest, sustained adaptation of autonomic control is a more likely mechanism of action. Previous short-term studies in the fetal sheep have shown that chronic hypoxia for just 24 to 48 h leads to progressive normalization of basal cardiac function but results in greater responses to acute events, consistent with augmentation of the chemoreflex (4). Furthermore, repeated hypoxia causes upregulation of immediate early genes in areas of the brain involved in regulation of sympathetic activity (10). Even in the adult human, acute hypoxia, but not hypercapnia, leads to long-lasting sympathetic activation (13). Central and peripheral factors are, of course, typically tightly coordinated, as shown by the observation that chronic intermittent hypoxia leads to an enhanced response to sympathetic stimulation, mediated by a decreased ability of NO to inhibit presynaptic norepinephrine release (9). Such studies demonstrate that programming results in complex and sustained alterations in physiological control mechanisms. What we now need to understand are the consequences of such alterations. The work by Broberg and colleagues has highlighted the concept that physiological “memory” of fetal experiences can have important influences on the adult heart, but, unlike other studies, they have shown that this can be beneficial. Of course, what determines whether such influences are in the long-term “good” or “bad” remains the fascinating question.

REFERENCES

