PERSPECTIVES

Novel mechanism causing restricted fetal growth: does maternal homocysteine impair placental amino acid transport?

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Determining the physiological mechanisms regulating fetal growth is critical for a better understanding of normal fetal development and the pathophysiology of abnormal fetal growth. Intrauterine growth restriction (IUGR) occurs when the fetus fails to reach its genetically determined growth potential. IUGR babies have a markedly increased perinatal morbidity, higher incidence of neuro-developmental impairment and increased risk of adult disease such as diabetes and cardiovascular disease (Hales *et al.* 1991; Barker *et al.* 1993). The primary determinant of fetal growth is the availability of nutrients, which is directly dependent on the transport functions of the placenta. The aetiology of human IUGR is complex, but a common theme in many cases of IUGR is an impaired placental nutrient transport. In a recent issue of *The Journal of Physiology*, Tsitsiou *et al.* (2009) reported experimental evidence for a novel mechanism by which placental amino acid transport may be reduced by elevated maternal homocysteine levels leading to IUGR.

Maternal hyperhomocysteinaemia is linked to IUGR; however the mechanism has not been established. Tsitsiou and coworkers hypothesized that homocysteine shares transport mechanisms across the placental barrier with neutral amino acids and, as a consequence, elevated homocysteine levels would impair placental amino acid transport by competitive inhibition. To address this possibility the authors carried out a series of carefully designed experiments in microvillous plasma membrane (MVM) vesicles isolated from the syncytiotrophoblast of the human placenta. This experimental system is highly appropriate and physiologically relevant since the uptake across this plasma membrane constitutes the active step of placental amino acid transport. By determining initial rate uptakes of isotope labelled substrates in the presence and absence of competing amino acids and performing kinetic analyses the authors demonstrate that three key transporters for neutral amino acids (Systems A, L, and y^+L) transport homocysteine with affinities similar to endogenous amino acids. Of particular importance, they established that System L constitutes the primary transport system mediating MVM homocysteine uptake.

In vivo placental amino acid transport may be impaired in IUGR through several distinct mechanisms. First, human IUGR is characterized by a reduced activity of placental transporters for neutral amino acids, including System A and L (Sibley *et al.* 2005). Second, placental amino acid uptake is critically dependent on the inwardly directed sodium gradient in the syncytiotrophoblast cell, which is maintained by Na^+,K^+-ATPase. MVM Na^+,K^+-ATPase activity is decreased in IUGR, which may result in an impaired driving force for placental amino acid transport *in vivo* (Johansson *et al.* 2003). Tsitsiou and collaborators have now identified a third, fundamentally different, mechanism that could contribute to impaired amino acid transport and development of IUGR *in vivo*.

They propose that increased maternal homocysteine levels, which are common in IUGR, competitively inhibit the placental transfer of endogenous amino acids. Their data suggest that hyperhomocysteinaemia preferentially would interact with the System L transporter, which is the primary mechanism by which essential amino acids such as leucine are transported to the fetus. This is of significance since the availability of essential amino acids is particularly important in stimulating fetal growth.

It is well established that an increased plasma concentration of homocysteine is an independent risk factor for cardiovascular disease. In addition, IUGR increases the risk of developing cardiovascular disease later in life. Thus, if maternal hyperhomocysteinaemia causes IUGR by inhibiting placental amino acid transfer, it provides a non-genetic mechanism by which susceptibility to cardiovascular disease may be transmitted between generations. Although the *in vitro* data of Tsitsiou *et al.* are very interesting, it remains to be demonstrated that moderate increases in maternal plasma concentrations, as observed in pregnant women, are sufficient to impair placental amino acid transport and fetal growth *in vivo*. Experiments in intact pregnant animals have the potential to reveal the true pathophysiological role of maternal hyperhomocysteinaemia in the development of IUGR.

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