Annotations

Placental transport: diversity and complexity

Every mammalian fetus is autonomous, being separated from its mother by a layer of fetal membranes. To allow nutrition, respiration, and excretion fetal blood flows through an extracorporeal circulation close to the mother's blood in the placenta. There are enormous and unexplained differences in placental architecture among species, more than are found in any other mammalian organ. In pigs the placenta is a simple corrugated membrane; in sheep it consists of some 50 individual miniplacentas. In both these species fetal and maternal blood remain mainly in capillary circulations separated by a multilayered epithelium formed of both maternal and extraembryonic fetal tissue. In human fetuses, by contrast, fetal blood flows through villi in which the capillaries are covered only by fetal tissue which bathes directly in the intervillous space in a pool of flowing maternal blood. Rat, mouse, and guinea pig placentas are similar, but these species have a subsidiary yolk sac placenta which transports immunoglobulin and which is absent in humans.

The outermost layer of the fetal membranes is trophoblast, which insulates the amnion, placental circulation, and fetus from the mother. Human trophoblast comprises several subpopulations of cells and also a syncytium.¹ It is metabolically active and contains enzymes which may be induced by maternal smoking and which can modify foreign compounds. It invades maternal tissue, but only to a controlled extent. Its limited expression of fetal histocompatibility antigens plays a part in the complex mechanisms that prevent rejection of the fetus by the mother. The trophoblast produces a wider range of hormones than any other tissue, and the large number of different receptors it bears on its surface for such molecules as insulin, epidermal growth factor, opioids, and catecholamines suggest that it may also function as an endocrine end organ. In addition, the placenta is an organ that carries out the transport tasks performed in postnatal life by alveolar epithelium, renal tubules, gut mucosa, and hepatocytes.

Transport mechanisms

There are several modes of transport across the placenta.^{2,3} Relatively lipid soluble molecules such as respiratory gases, anaesthetic agents, many other

drugs, and unconjugated bilirubin cross easily by penetrating the cell membranes of the placenta. Small water soluble molecules such as urea and water itself also cross easily down diffusional or osmotic gradients and may do so through minute pores of molecular dimensions^{4,5}; these, however, have not been convincingly shown by electron microscopy and are a little difficult to reconcile with the syncytial nature of human trophoblast because in other tissues pores are usually between cells. Small electrolytes may also cross by this route. Transfer of glucose is markedly facilitated by a specific carrier molecule, but it is not actively transported. Most amino acids, calcium, and perhaps potassium and phosphate, are transported from mother to fetus by specific carrier mediated processes, but these—unlike that for glucose—consume energy and carry out active transport, leading to higher concentrations in fetal than maternal plasma. Immunoglobulin G (but not A, M, or E), iron, and vitamin B₁₂, are taken into the trophoblast by receptor mediated endocytosis and then released by a poorly understood mechanism into the fetal circulation.

Diversity among species means that simple extrapolations from experimental animals to women are not permissible but many mechanisms are the same in different species—for example, the carrier systems for calcium, amino acids, and glucose. Other transport systems, such as those for iron or for immunoglobulin, may be radically different as is the passive permeability to less soluble drugs. Animal studies are better used for building up a clear picture of how placental transport works as a whole rather than for answering specific clinical questions, though the latter is often unwisely attempted.

Control of placental transfer

Little is known about the control of placenta permeability. The rate of transfer of highly permeable lipid soluble molecules such as those mentioned above is not affected by thickening or thinning of the placental tissue barrier but rather by the rate of blood flow in maternal and fetal circulations and by their geometrical relationship to each other. Their transfer is said to be 'flow limited'. Large increases in placental blood flow as gestation proceeds are

important so that the transport of respiratory gases can be increased to meet the needs of the growing fetus. Short term modulation of blood flow does not seem to be an important physiological control mechanism, but reductions may reduce gas transfer in disease.

The permeability of lipid insoluble substances which cross more slowly is hardly affected by changes in the rate of blood flow. Their passage is, by contrast, 'membrane limited' and any control of their transfer is likely to be by a change in placental tissue carrier mechanisms. An example of membrane limited control in the placenta is the ability of the rat placenta to keep a fetus normokalaemic when the mother is hypokalaemic,⁶ and there are hints of similar mechanisms for calcium and for amino acids. The ability of the pig placenta to increase sodium transport towards the fetus under the influence of fetal catecholamine in vitro may represent another control process.⁷ It is not known if controls such as these are important in humans.

Transport and disease

It seems certain that abnormalities of placental transport contribute to fetal disorder, but there is little direct evidence to support this—apart from the general association between the placenta's poor growth, abnormal histology, and disturbed endocrine function, and some cases of intrauterine growth retardation and maternal gestational disease. Maybe we have not always looked at the right conditions. Spontaneous abortion or fetal death, congenital malformation, transient perinatal diseases such as non-immune fetal hydrops or neonatal hypocalcaemia, or problems not apparent until later childhood (such as cerebral palsy) might all reasonably on occasion be attributable to placental transport defects, but we have no direct evidence for this. Normal transport of unwanted maternal plasma constituents—IgG leading to neonatal disease, or fetal heart block in maternal immune disease, or fetal infection by those viruses which affect the fetus before term—might

also be preventable if we could develop means of manipulating placental transport mechanisms.

To progress the techniques now becoming available must be applied: amniocentesis (though amniotic fluid constituents, notably proteins, may reflect maternal rather than fetal plasma),⁸ placental villous biopsy, non-invasive placental imaging and blood flow studies, heavy isotope techniques, and the ability to sample fetal blood in utero before labour.⁹ Each of these approaches, however, provides only one piece of a complicated jigsaw puzzle. For satisfactory evaluation of the data they provide, their use must be linked to a clear understanding of placental physiology and to an alertness that a placental defect might be the cause of a specific clinical problem in the fetus, newborn, or older child.

References

- ¹ Loke YW, Whyte A. eds. *Biology of trophoblast*. Elsevier: Amsterdam, 1983.
- ² Faber JJ, Thornburg L. *Placental physiology*. Raven Press: New York, 1983.
- ³ Morriss FH, Boyd RDH. *Placental Transport* In: Knobil E, Neill JD, eds. *The physiology of reproduction*. Raven Press: New York (in press).
- ⁴ Willis DM, O'Grady JP, Faber JJ, Thornburg KL. Diffusion permeability of cyanocobalamin in human placenta. *Am J Physiol* 1986;**250**:459–64.
- ⁵ Bain M, Landon MJ, Copas DK, Stacey TE. Permeability of the human placenta in vivo. *Early Hum Dev* 1986;**14**:137–8.
- ⁶ Dancis J, Springer D. Fetal homeostasis in maternal malnutrition: potassium and sodium deficiency in rats. *Pediatr Res* 1970;**4**:346–51.
- ⁷ Sibley CP, Ward BS, Glazier JD, Moore WMO, Boyd RDH. Electrical activity and sodium transfer across in vitro pig placenta. *Am J Physiol* 1986;**250**:474–84.
- ⁸ Super M, Fennell SJ, Schwarz MS, Boyd RDH. Investigation of cholinesterase in amniotic fluid. *Br Med J* 1986;**293**:17–8.
- ⁹ McIntosh N, Rodeck CH, Heath R. Amino acids in the mid-trimester human fetus. *Biol Neonate* 1984;**45**:218–24.

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