CURRENT TOPIC

Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis

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Fetal origin of adult diseases

Epidemiological studies have shown a close correlation between intrauterine growth retardation (IUGR) and the onset of insulin resistance, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, hyperlipidaemia, and cardiovascular diseases in adult life.[1–6] To explain this association, the concept of re-programming has been introduced: intrauterine exposure to insufficient nutrient supply during critical periods of fetal life would permanently affect the development and function of the endocrine system, leading to metabolic changes, including reduced insulin sensitivity.[5 6]

Although knowledge of the mechanisms involved in the re-programming process might allow new strategies for early prevention of long term metabolic disturbances to be developed, the pathophysiological link between fetal growth impairment and adult diseases is still unclear.

The "thrifty phenotype" and the "fetal salvage" hypotheses

In 1992 Hales and Barker[7] proposed the model of the "thrifty phenotype," suggesting that intrauterine malnutrition would lead to insulin resistance and decreased β cell mass, thus predisposing to NIDDM. According to this hypothesis, the endocrine alterations induced by intrauterine malnutrition are intended to divert the limited nutrient supply to maintain survival and development of vital organs, such as the brain, at the expense of growth.

More recently, the "fetal salvage" hypothesis has been formulated.[8] The finding that prepubertal IUGR children show a far greater insulin response than normal birthweight children, challenges the previously proposed β cell hypoplasia.[9] The "fetal salvage" model suggests that the malnourished fetus develops peripheral insulin resistance which allows a redistribution of nutrients, such as glucose, in favour of essential organs. This then leads to a permanent reduction in skeletal muscle glucose transporter number or function. This reduced peripheral insulin sensitivity stimulates β cells to produce larger amounts of insulin to achieve normal glycaemia and would lead to eventual β cell exhaustion. This hypothesis is supported by studies in animal models showing reduced glucose transporter protein concentrations in skeletal muscles of IUGR fetuses and normal concentrations in the brain.[10 11]

Insulin-like growth factors: more than modulators of growth

The insulin-like growth factors (IGFs)-I and -II are structurally related to insulin, bind to specific receptors (type 1 and 2 IGF receptors) and, with lower affinity, to insulin receptors. IGFs circulate in blood bound to a family of at least 10 different binding proteins (IGFBPs) that regulate the biological activities of the IGFs, also exerting IGF independent actions.[12–14] The affinity of IGFBPs for IGFs can be reduced by specific IGFBP proteases which, by fragmentation of IGFBPs, lower the binding of IGFs and increase IGF bioavailability.[15] IGFs exert primarily growth promoting and insulin-like actions. IGF-I administration to humans affects glucose metabolism, stimulating glucose uptake and leading to hypoglycaemia. At higher concentrations, IGFs can bind to insulin receptors and the administration of IGFBP-1, a known inhibitor of IGF biological actions, increases glucose concentrations.[16]

A role for IGFs in fetal growth is suggested by numerous observations. A close correlation between umbilical cord serum IGF-I concentrations and birthweight has repeatedly been reported.[17–19] IGF-I and IGFBP-3 concentrations are reduced in IUGR children, but IGFBP-1 and IGFBP-2 concentrations are increased in samples obtained in utero and cord serum.[20 21] Targeted mutagenesis of the genes encoding IGF-I and -II and type 1 IGF receptor induces profound embryonic, fetal, and postnatal growth retardation in mice.[22 23] The first patient with severe IUGR and postnatal growth retardation caused by a deletion of IGF-I gene has been described.[24] Finally, the increased IGFBP-3 proteolytic activity found in mothers with multiple fetuses or fetuses affected by uteroplacental insufficiency suggests a plausible mechanism for the increased IGF bioavailability whenever fetal growth is threatened.[25]

We recently observed the presence of at least two different IGFBP-3 proteases in the serum of IUGR children, the role of which might be the amplification of the IGF growth promoting action which determines early postnatal "catch-up" growth in most IUGR infants.[26]

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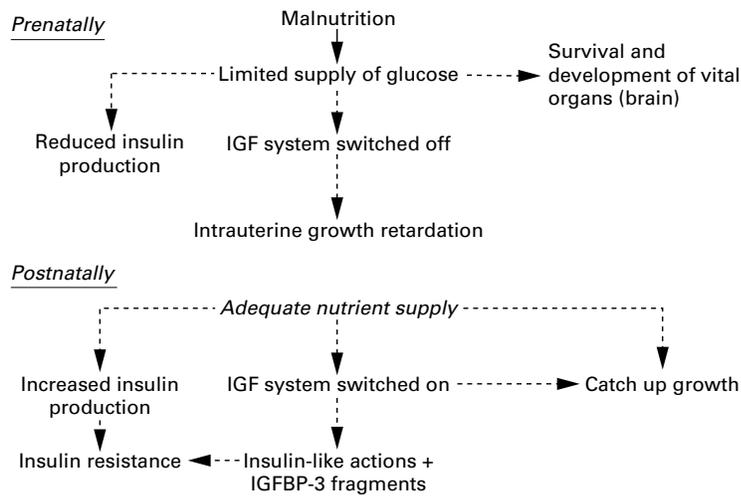Email:
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Figure 1   Schematic representation of "catch-up growth" hypothesis. Adequate postnatal nutrient supply activates IGF system, leading to catch-up growth and insulin resistance. IGF: insulin-like growth factor; IGFBP-3:insulin-like growth factor binding protein-3.

The "catch-up growth" hypothesis

IUGR children show a rearrangement of the endocrine system at birth, having low concentrations of insulin, IGF-I, IGFBP-3, and high concentrations of growth hormone, IGFBP-1, and IGFBP-2. Normalisation of these parameters occurs during the first trimester of postnatal life.[26 27] It is conceivable that tissues chronically depleted of insulin and IGF-I during fetal life and suddenly exposed to increased concentrations of the two hormones shortly after birth, may counteract their additive insulin-like actions by developing insulin resistance as a metabolic defence mechanism to protect the organism from hypoglycaemia. According to this model, the crucial time for the development of long term consequences is early postnatal life when catch-up growth occurs in around 80% of IUGR children.[28] Consistent with our hypothesis, data from animals have shown that when fetal growth impairment is followed by catch-up growth postnatally, the lifespan is significantly shortened.[29] Moreover, the glucose induced insulin response in infants with catch-up growth is higher than that in children without significant catch-up growth.[30] Therefore, those IUGR infants who show early and complete recovery from intrauterine growth retardation would be at higher risk for the occurrence of metabolic disturbances like insulin resistance and NIDDM in adulthood (fig 1).

In addition, the recent demonstration of the ability of IGFBP-3 fragments generated by proteolytic cleavage to bind insulin, inhibiting binding and activation of insulin receptor,[31] suggests that the increased IGFBP-3 proteolytic activity observed in the first months of life of IUGR children might contribute to the development of insulin resistance (fig 1).

Finally, Whitaker and colleagues have recently reported that an early "adiposity rebound," the point of maximal leanness usually achieved at 5 to 6 years of age, is associated with an increased risk of adult obesity.[32] Early "adiposity rebound" has been suggested as constituting a marker for growth acceleration

and cell hyperplasia[33] which are, at least transiently, exaggerated during catch-up growth in IUGR infants who therefore might have an additional risk of developing insulin resistance in adulthood.

In conclusion, we speculate that the tremendous effort to recover height shortly after birth, involving overactivation of the IGF system kept quiescent during intrauterine life to divert the restricted nutrient supply from growth to survival of vital organs, induces a metabolic adaptation with long term effects. The secondary insulin resistance, when associated with other risk factors such as genetic predisposition or obesity, may eventually lead to NIDDM which would thus represent a potential long term consequence of catch-up growth in IUGR children.

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