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Lifelong consequences of metabolic adaptations in utero?

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Dr. Phillips is advocating the interesting view point that undernutrition during intrauterine development predisposes the fetus to insulin resistance in adult life. He suggests that the undernourished fetus makes metabolic adaptations from which it benefits in the short term by increased fuel availability but that these adaptations become permanently programmed and persist throughout life. The basic arguments in favour of this notion are mainly epidemiological in character. Impaired glucose tolerance in young children and (non-insulin-dependent) diabetes mellitus in middle-aged individuals have been shown to be associated with low birth weight [1–3], and, more precisely, with disproportionate growth, i.e. thinness at birth as shown by a low ponderal index (weight/length^3) [4, 5]. An association between low birth weight and insulin resistance in adult life has also been detected in Mexican-Americans [6] and Pima Indians [7], thereby providing evidence that the proposed relationship could be of a more general nature.

Proposed mechanism

If the existence of a statistical association between low birth weight and impairment in glucose tolerance in later life may be regarded as established, and a *causal relationship* between the intrauterine and adult events can be surmised, the cell biological nature of such a relationship is less well characterized. In other words, *why* and *how* would an embryo change its metabolism in this way – and conserve this change for a whole lifetime? What are the immediate teleological advantages, as well as the more long-term benefits? How is this metabolic change brought about? When the author sets out to answer these questions he is treading on rather thin scientific ice. The suggested aetiologic mechanism for the adult insulin resistance/impaired glucose tolerance entails a primary reason for undernutrition during intrauterine life, e.g. placental insufficiency or low maternal levels of nutrients. The starving conceptus then alters its metabolism in response to the shortage of nutrients. The important alteration is "glucose sparing" where the embryo learns to oxidize other substrates, amino acids, fatty acids, and lactate, rather than glucose. As one consequence, amino acids are shunted from protein biosynthesis to energy production, the fetus maintains normal linear growth at the expense of reduced growth of fat and muscle [8]. Surprisingly, these babies seem to catch up in their growth postnatally [9], although the "glucose-sparing" metabolism in the small-for-gestational age neonates may persist into adult life and lead to insulin resistance.

Direct studies of the metabolic aspects of the suggested syndrome are relatively scarce. In clear support of the notion of impaired adult glucose handling in small-for-gestational age neonates, are the investigations using ^{31}P magnetic resonance techniques. These studies have demonstrated that small-born subjects have lower rates of glycolysis and glycolytic ATP production in response to an oral glucose load [10]. Other investigations have indicated that the impaired glucose tolerance is not associated with either decreased insulin secretion in adult age [3], or with a disturbed metabolism of non-esterified fatty acids (NEFA) and triglycerides [11]. The metabolic link between the intrauterine insult and adult insulin resistance remains elusive.

Future research directions

The notion of an intrauterine origin of adult impairment in glucose homeostasis is an exciting hypothesis,

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although its developmental and physiological foundation could be stronger. In order to delineate the aetiologic mechanisms two approaches for future research can be envisaged. The first is non-human, and would attempt to answer the question: can this suggested series of metabolic events be copied in a species other than *Homo Sapiens?* In other words, are there any confirmatory animal models available? A preliminary answer would be more negative than positive, at least with regard to models of an intrauterine insult and subsequent disturbance in the glucose homeostasis of the offspring. Protein malnutrition during pregnancy in rats yields offspring with impaired glucose tolerance in adult life, but this effect is mainly ascribed to decreased insulin secretion and not to increased insulin resistance [12, 13]. Impaired activity of the pancreatic beta-cell mitochondrial enzyme glycerophosphate dehydrogenase has been found in islet homogenates from these glucose intolerant rats, which may be of importance for the impaired beta-cell function [14]. A defect in insulin secretion is also present in adult rats subjected to a period of protein malnutrition during the immediate postnatal period [15], as well as in the growth-retarded offspring of rats with surgically ligated uterine arteries [16, 17]. The experimental data, therefore, seem to rule out a direct parallel between human (proposed) early malnutrition and experimental malnutrition in rodents. On the other hand, in the adult offspring of severely diabetic rats insulin resistance has been demonstrated [18], mainly confined to skeletal muscle and liver [19]. This finding has been further corroborated by a study of the offspring of manifestly diabetic rats given intense insulin treatment during the latter part of pregnancy [20]. In this in vitro investigation the offspring were insulin resistant at 4 and 6 months of age, with no effect on insulin secretion, or pancreatic insulin content. Furthermore, there was a clear-cut gender difference, since the males were more insulin resistant than the females [20]. It thus seems that in rat models protein malnutrition during gestation leads to impaired insulin secretion in later life, whereas manifest diabetes in the mother yields insulin resistance in the adult offspring; truly intriguing results. Of particular interest in this context is that manifest diabetes in the rat yields increased maternal levels of several key nutrients [21], as well as an elevated blood flow to the implantation site in early pregnancy [22]. Full understanding of the proposed intrauterine origin of adult insulin resistance, therefore, demands the demonstration of a common denominator between the undernourished human offspring and the overnourished rodent offspring in the manifest diabetic uterus, both of which develop insulin resistance in later life. Such an understanding may certainly be of importance when considering the rodent models of gestational malnutrition and their effect on the offspring [23], for instance the described alterations in liver function and structure allowing the organ to produce glucose rather than to metabolize and store it [24].

The other research approach is human, and should attempt to scrutinise the heart of the metabolic problem, the question what is wrong with the babies showing disproportionate growth in late gestation? Which is the principal metabolic pathway or hormonal response that a maternal diabetic environment may reschedule in the offspring? Obviously it is neither insulin secretion, nor NEFA or triglyceride metabolism. The thin, small-for-age, newborn infant may be the youngest pre-diabetic patient we will ever encounter, therefore it certainly is important to find the principal change that these babies should be screened for, be it enzymatic or hormonal. Studies of the dynamics of the metabolic disturbance – which appears to be aggravated with time – should be performed to suggest therapeutic actions preventing an impaired glucose tolerance in adult life.

Summary

Dr. Phillips argues that insulin resistance in adult life may be the price the developing fetus has to pay in return for a short-term successful adaptation to undernutrition in utero. The concept is interesting, and, indeed, challenging. There is, however, a strong need for expansion of the existing knowledge of the possible developmental mechanisms involved, especially against the background of the obvious diagnostic and therapeutic gains in this particular group of patients.

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