Metabolic programming: fetal origins of obesity and metabolic syndrome in the adult

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The results of recently reported investigations (14) have shed new light on our understanding of “metabolic programming” by nutrients and its relation to adult-onset obesity and its potential reversibility (14). The topic is especially germane, considering the world-wide rise in the incidence and prevalence of obesity, metabolic syndrome, and type 2 diabetes, which are increasingly being characterized as an epidemic. The concept of metabolic programming is not just a curiosity observed in experimental rodent models and is highlighted by the rapidly accumulating epidemiological evidence from human studies that have been pioneered by Barker (1). There is now strong evidence that fetal undernutrition (due to protein malnutrition in the mother or to a host of other causes) is associated with subsequent coronary artery disease during adult life (3, 5). The “fetal origins” hypothesis has been verified and extended by others (7, 10, 11) to include evidence of association between low and high birth weights with maternal body mass index (BMI) and with an increased risk for metabolic syndrome, coronary heart disease, and obesity. The mechanisms that lead to obesity and metabolic syndrome are complex and multifactorial and include genetic and maternal determinants.

Patel et al. (8) have adapted the method of artificially rearing rat pups (“pup-in-a-cup” model) described by Hall (6) to determine the effect of dietary composition on newborn rats reared from postnatal day 4 through day 24. The animals were fed one of two types of diets (both at 0.45/g body wt/day): a diet that is similar in composition to rat milk and is rich in fats (high-fat, HF; 68% of calories derived from fat, 24% from protein, and 8% from carbohydrates) or a diet rich in carbohydrates (high carbohydrate, HC; 20% of calories derived from fat, 24% from protein, and 56% from carbohydrates, mostly polysaccharide). They also compared the results with another control group of pups reared by their dams (mother fed, MF). The pups receiving the HC diet (1-HC rats) exhibited a number of profound metabolic changes that became evident during the 20-day artificial feeding period and persisted during their adult life. These 1-HC pups rapidly developed hyperinsulinemia (a 2- to 3-fold increase in blood insulin levels as early as 6 days of age). There was also a large increase in the number of small islets containing a higher percentage of insulin-positive cells associated with an increase in the total mass of β-cells (8, 9, 12). These islets secreted an excessive amount of insulin at normal concentrations of glucose; in addition, they exhibited a number of metabolic changes, including higher-than-normal levels of GLUT2, hexokinase, and the transcription factor pancreatic duodenal homeodomain-1 (PDX-1) (8, 12). The pups fed the 1-HF diet had none of these changes and were similar to the 1-MF-fed pups. All the pups were weaned at 24 days, after which they consumed rat chow ad libitum. The 1-HC pups continued to be hyperinsulinemic, and after 50 days excessive weight gain became evident; they consumed 10–15% more food, and their body mass was 15–25% greater than that of 1-MF or 1-HF rats by 4 mo. Although these 1-HC rats did not become hyperglycemic, their serum triglyceride levels were increased two- to threefold compared with the 1-MF controls (8). The obesity noted in these rats may well be the result of the chronic hyperinsulinemia.

Of great interest is the observation that the 1-HC females (but not males) passed on much of the above metabolic phenotype to both their male and female offspring (13, 15). Pregnant 1-HC females, consuming normal rat chow, continued to have elevated levels of insulin and triglycerides in their blood. They delivered normal-appearing pups (labeled as 2-HC rats), which were then reared by the 1-HC dams or by foster dams. In either case, the 2-HC rats were hyperinsulinemic and had several of the same abnormalities in their islet morphology and metabolic functions noted above. These changes occurred early in the postnatal period and persisted into adulthood. Compared with MF controls, the 2-HC rats began to develop obesity, similar to their 1-HC mothers, at ~50 days of age (8, 13, 15) and had elevated plasma levels of insulin and triglycerides with no alteration in the concentration of plasma glucose. This is an excellent example of metabolic programming of the newborn by alterations in the composition of the diet during the postnatal developmental phase of the previous generation.
In their most recent study, Patel and colleagues [Srinivasan et al. (14)] have extended our understanding of the critical importance of nutritional patterning of the mothers for fetal and postnatal development of their pups by pair-feeding the 1-HC and 1-MF female rats from 24 days into puberty and beyond. The 1-HC pups had been artificially fed the HC milk formula from postnatal day 4, as described above. Food intake of the 1-HC rats starting from postnatal day 24 was restricted by pair-feeding to age-matched 1-MF female rats (amounting to reduction in daily food intake of ~15% from the ad libitum intake of 1-HC rats). Both groups of rats were fed normal rodent chow with 11% of calories derived from fat, 19% from protein, and 70% from carbohydrates. When food was restricted, the 1-HC rats failed to gain excessive weight, and as adults they had normal insulin and triglyceride levels. Importantly, the pair-fed 1-HC females gave birth to pups that grew normally without exhibiting any tendency toward obesity or hyperinsulinemia. The results clearly establish the “plasticity” and reversibility of the model and demonstrate the critical role of dietary intervention in controlling obesity and metabolic syndrome.

A number of questions remain unanswered by these studies. It is not clear, for example, whether the calorie restriction of the 1-HC rats, which was implemented at 24 days, would have been as effective if it had been applied at a later stage of development (i.e., once increased weight gain had begun). The biochemical mechanisms responsible for the development of hyperinsulinemia, overeating, and obesity in the 1-HC and 2-HC rats remain to be resolved. What is there about the HC diet that leads to the abnormalities in the 1-HC pups and rats? Is it the carbohydrate in the HC formula or the hyperinsulinemia induced by the HC formula that leads to the 1-HC phenotype? Are there set-point changes in metabolic processes in the islets and/or in the hypothalamus that control satiety; if so, what are they and how are they modified? How does the pregnant 1-HC rat confer the hyperinsulinemia and obesity phenotype to her offspring? Clearly, 1-HC dams are obese and exhibit high levels of insulin and triglycerides, and they undoubtedly have abnormal levels of a myriad of known and unknown cytokines and adipokines that may affect the developmental program of the 2-HC pups in utero. Identification of the signals and the biochemical mechanism underlying this metabolic programming requires active pursuit. It is also interesting to note that, although serum triglyceride concentrations were increased in both 1-HC and 2-HC rats, there was no significant increase in glucose concentrations. Therefore, does programming in this model, or the metabolic perturbation during lactation, preferentially affect lipid and not glucose metabolism?

Another important question raised by this study is its relevance to human metabolism and to the rising incidence and prevalence of obesity in populations throughout the world. Although these studies involve rats, the metabolic condition of the 1-HC pregnant females is similar to that of obese pregnant humans. Overweight pregnant women are markedly hyperinsulinemic, often have elevated triglycerides, and probably have abnormal levels of many of the same cytokines and adipokines noted in obese pregnant rats. The biochemical mechanisms that are responsible for the proposed metabolic programming in humans need to be closely examined. Carefully designed longitudinal studies could verify and extend the association between the mother’s BMI and other phenotypic characteristics with those of the newborn, both during their fetal stage and later during their adulthood. The potential of applicability of the findings to humans, however, requires an understanding of the differences in fetal growth in the two species. The prevention of the obese phenotype in the 1-HC rats began with pair feeding beginning at postnatal day 24, well before the development of obesity at day 50. In the human fetus, there is significant accumulation of body fat in utero (10–12% of body mass and among the highest in mammalian species); the accumulation of fat is potentially greater when the mother is obese or has diabetes (2, 4). Therefore, the modification of diet may need to be initiated during gestation as well as during lactation in these high-risk women. Considering these and other interesting questions, it is likely that the animal model being studied by Patel and colleagues can provide important clues to the factors responsible for diet-induced obesity and metabolic syndrome in humans.

REFERENCES