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COMMENTARY

Surprising? Perhaps Not. Long-Chain Fatty Acid Oxidation during Human Fetal Development

Commentary on the article by Oey *et al.* on page 755

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One of the dogmas in fetal and perinatal medicine and fetal and perinatal animal research and thought is that the fetus relies solely upon the constant supply of maternal glucose *via* the placenta to generate energy for essential functions and growth (1). A corollary to this "glucose only" dogma is that the placenta, which carries the fetal genome, also utilizes glucose as the major energy substrate (2). In this scenario, because mammalian milk contains the majority of its nutrients as fat, the fetal-to-neonatal transition requires a very rapid adaptation or switch from glucose to fat as the major nutrient.

In the last 20 y, the discovery and characterization of recessively inherited disorders in the more than 20 genes of the mitochondrial fatty acid oxidation pathway have renewed interest in fatty acid metabolism because these disorders cause early morbidity and mortality in affected infants with phenotypes of hypoketotic hypoglycemia and liver dysfunction, cardiomyopathy, multiorgan failure, and sudden infant death (3,4). Because these phenotypes are intermittent and occur in infants subjected to stresses that activate or require fatty acid oxidation (FAO), such as fasting, infection, and exercise, and because fatty acid metabolites, such as acyl-carnitines, accumulate in body fluids and tissues, two pathogenetic mechanisms for FAO disorders have been postulated. The first, the "energy deprivation" hypothesis, suggests that a lack of sufficient energy production, especially in the highly oxidative tissues that rely upon FAO such as heart and skeletal muscle, causes the phenotype. The second, the "toxic metabolite" hypothesis, suggests that accumulation of fatty acid intermediates results in organ dysfunction by some as yet ill-defined toxic mechanism. Data to support both hypotheses exist. However, a recent observation has provided potential insight into the pathogenesis of FAO disorders and may be more consistent with the toxic metabolite hypothesis (5–7).

That is, over the last 10 y, a unique maternal-fetal interaction has been noted in families with a subset of FAO disorders. During pregnancies of women carrying fetuses affected with long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) or general trifunctional protein (TFP) deficiency secondary to mutations in either of the closely linked α- or β-TFP genes that encode the two subunits of the heteroctameric TFP complex, the heterozygote mothers often develop life-threatening liver diseases, including acute fatty liver of pregnancy (AFLP), the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, or preeclampsia. The cause of this association was postulated as accumulation of toxic fatty acid metabolites in the maternal circulation. If, however, the "glucose only" dogma were correct, the toxic metabolite accumulation hypothesis to explain the occurrence of maternal liver disease in LCHAD or TFP deficiency would not be tenable, simply because the absence of fetal FAO would not produce any "toxic metabolites." To explore the pathogenesis of this unusual association, several laboratories were, therefore, prompted to reevaluate of the role of FAO in placental and fetal metabolism (8–10). Using a variety of approaches, including assessment of FAO enzyme activities in placenta and fetal tissues, immunoblot studies to examine FAO enzyme expression, and measurement of overall FAO in placental tissue slices or cytotrophoblast cells, research teams headed by Michael Bennett, Arnold Strauss, and Ron Wanders have previously shown that active FAO enzymes are expressed in substantial amounts in human placenta and that FAO flux indeed occurs. These previously published results contradict the "glucose only" hypothesis described above, at least for the fetally derived placenta. In this issue of *Pediatric Research*, the Dutch group has gone even further and clearly demonstrated that very-long-chain acyl-CoA dehydrogenase (VLCAD), carnitine palmitoyltransferase 2, and LCHAD mRNA and enzymatic activity are substantial in many fetal tissues, including liver, retina, and heart, even early in gestation (11). The measured fetal cardiac and hepatic enzyme activities were similar to those present in adult human liver and higher than in adult skeletal muscle, consistent with the idea that fetal FAO is comparable in some tissues to adult FAO, a remarkable suggestion. This extraordinary finding demonstrates that human fetal FAO can and does occur even early in gestation. What does this surprising finding imply?

The obvious conclusion is that FAO is a significant component of fetal and placental metabolism and energy production. The Dutch data also show that developmental and tissue-specific expression of FAO enzymes occurs, with higher levels of VLCAD mRNA in liver than in heart, kidney, or gut at 45 d

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gestation. Very high levels of expression in heart and retina in very early gestation (35 d) were noted (11). These results imply that tissue-specific regulation of expression occurs, as is apparent in postnatal life. If FAO is a prominent source of fetal and placental energy, it is apparent that accumulation of toxic long-chain fatty acid metabolites in fetal and maternal circulations is possible in infants deficient in LCHAD or TFP. The need for further studies to define percentages of ATP derived from fat *versus* glucose oxidation in fetal tissues is suggested by these results. It seems apparent then, that the "glucose only" dogma is untenable, and that fetal and placental FAO are important for fetal survival and maintenance of pregnancy. This surprising conclusion should revolutionize our thinking about the metabolic state of the maternal fetal unit and the importance of fat in its well being.

A second obvious conclusion is that these results support the "toxic metabolite" hypothesis as the cause of maternal liver disease in fetal FAO. That is, maternal liver disease does NOT occur when heterozygote mothers are pregnant with genetically normal or LCHAD or TFP heterozygote fetuses (5). Therefore, it is the fetal and placental genotype that determines and "causes" maternal illness. If this "toxic metabolite" hypothesis is correct, there is an obvious need to measure accumulation of such metabolites in maternal and fetal body fluids and tissues during affected human pregnancies. That is, which metabolites accumulate and how and why are these toxic to the mother?

However, these recent results from several laboratories proving that fetal FAO occurs raise additional intriguing questions and may not be so surprising. Among the human FAO disorders, fetal deficiency of LCHAD and TFP is commonly associated with maternal AFLP, HELLP, and preeclampsia. In contrast, VLCAD deficiency, another long-chain FAO defect, is never associated with maternal liver disease, and fetal MCAD deficiency has only very rarely been reported associated with maternal HELLP syndrome (12). If fetal FAO deficiency with a decreased ability to generate energy (the "energy deprivation" hypothesis) and accumulation of toxic long-chain metabolites (the "toxic metabolite" hypothesis) were the sole cause of maternal liver disease, why does this not occur in VLCAD or MCAD deficiency? Clearly, the results are inconsistent with the "energy deprivation" hypothesis. But, abnormal fatty acid metabolites must accumulate in fetal VLCAD or MCAD deficiency as well, so it is very uncertain as to the mechanisms of causation of maternal liver disease. Is it because the "toxic metabolites" are different in LCHAD or TFP deficiency in which long-chain 3-hydroxy-fatty acyl derivatives occur than in VLCAD or MCAD deficiency? Might the 3-hydroxy-fatty acids be more toxic? If so, what is the mechanism of toxicity? It remains disconcerting that only some of the fetal FAO disorders are associated or cause maternal liver disease and not others.

My highly speculative hypothesis to explain this conundrum is that LCHAD and TFP may have additional functions other than their enzymatic roles in the FAO pathway. The human genome project now suggests that as few as 20,000 genes comprise the total complement of our genome. It has been suggested that, therefore, many gene products must have multiple functions (13,14). That is, in addition to their known roles in, for example, metabolism, some genes may "moonlight" in other roles than their primary enzymatic function. Might fetal LCHAD or TFP serve a regulatory role in fetal (and adult) metabolism by being sensors of normal or aberrant fatty acid intermediates, such as long- or medium-chain acyl-CoAs? Might interactions of these normal and abnormal metabolites, much as malonyl-CoA is known to regulate carnitine palmitoyl-transferase I activity, with LCHAD alter mitochondrial functions other than FAO? For example, TFP is associated with the inner mitochondrial membrane and might serve a structural role in maintaining the integrity of this highly complex structure. Deficiency of LCHAD might interfere with function of the ADP-ATP translocator, alter cardiolipin metabolism, or disrupt the complexes of the electron transport chain, for example. Fatty acids are critical regulators of the peroxisomal proliferator–activating receptors (PPAR) and other members of the nuclear hormone receptor superfamily of transcription factors (15). Might binding of abnormal metabolites by LCHAD or TFP sequester these metabolites away from activation of PPAR and alter a whole program of downstream PPAR-regulated genes? In the fetus and placenta, for example, might this fatty acid regulatory pathway be disrupted in LCHAD deficiency, but not in VLCAD deficiency?

The results reported in *Pediatric Research* by the Dutch group and other previously published results (8–11) prove conclusively that FAO can and does occur in human placenta and human fetal tissues. This result is surprising and abrogates the "glucose only" hypothesis. The data suggest that the association of some FAO disorders with maternal liver disease may be explained by the "toxic metabolite" hypothesis as placentally and fetally derived fatty acids might poison the maternal liver. Nonetheless, as often happens in science, the results also raise intriguing questions that require further investigation, perhaps suggesting the LCHAD or other FAO enzymes might have additional, nonenzymatic roles in human development.

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