commentary

Lipotoxicity: what is the fate of fatty acids?[1]

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Accumulation of lipid in nonadipose tissues plays a critical role in the pathogenesis of a diverse array of chronic diseases, including diabetes and heart failure. Normal cellular homeostasis relies on a critical balance of fuel uptake and utilization that is controlled by elaborate transcriptional networks, which ensure that cellular energy needs are consistently met and toxic intermediates do not accumulate. This process is particularly important for the heart, which has a continuous high energy demand. The heart meets this demand by dynamically shifting its preference for glucose and fatty acids in various physiologic and pathologic circumstances. This change is driven by alterations in signaling networks and regulated expression of key metabolic genes. While the heart predominantly relies on fatty acids as a fuel source, under normal conditions the myocardium is not a site of significant lipid storage. Moreover, conditions that promote fatty acid excess, such as insulin resistance and diabetes, are associated with detrimental effects on cardiac function. Evidence has emerged that fatty acid overload may damage the myocardium through excessive fatty acid oxidation and accumulation of toxic lipid species within the myocardium. These toxic effects have been termed "lipotoxicity" (1). A number of investigators have implicated specific lipid species, such as long-chain saturated fatty acids (palmitate), in the pathogenesis of cardiomyocyte dysfunction (2, 3), while unsaturated fatty acids (oleate) are considered cardioprotective (4).

The mechanism whereby some fatty acid species exert more toxic effects than others is poorly understood. In this issue of *The Journal of Lipid Research*, Lockridge et al. (5) report microarray data of the differential effects of several fatty acid species in adult cardiac myocytes. Previous investigations have primarily evaluated direct effects of individual fatty acid species in neonatal rat cardiac myocytes, where the expression of key metabolic regulators is still changing. Thus, the work by Lockridge et al. provides new insight into effects in a mature cardiac myocyte and does this in a systematic and unbiased manner.

The most striking finding in this study was the dramatic effect of the long-chain saturated fatty acid palmitate on gene expression for enzymes involved in the endoplasmic reticulum (ER) stress response and apoptosis pathways as well as markers of DNA damage. These findings are consistent with other recent data in CHO cells, in which palmitate was found to be trafficked to the ER and to have dramatic effects on ER structure and integrity as well as to disrupt mitochondrial function (6). Furthermore, ER stress has been implicated in apoptosis of pancreatic β cells from type 2 diabetic models (7). Taken together, this recent evidence strongly implicates ER stress in the cellular dysfunction associated with palmitate exposure. Further studies specifically evaluating the ER stress response in cardiac myocytes will be important in understanding the mechanisms of cardiac dysfunction associated with lipid overload and in targeting potential therapies to alleviate cardiomyopathy associated with diabetes.

Interestingly, Borradaile et al. (6) also found that induction of fatty acid oxidation minimized the effects on ER integrity upon exposure to palmitate. Lockridge et al. (5) demonstrated differential effects of oleate versus palmitate on gene expression for a number of enzymes that play a role in upregulating mitochondrial fatty acid oxidation pathways (e.g., *Cpt1a*, *Fatp1*, and *Ucp3*). While palmitate also upregulated many components of mitochondrial oxidative pathways, the more robust effect of oleate on some of these genes is intriguing. One of the genes the authors highlight that is specifically induced by oleate is *Ucp3*. They suggest that upregulation of *Ucp3* may result in increased recycling of free CoA and thus promote the oxidation of oleate, whereas palmitate may be more likely to accumulate in the mitochondria, leading to cytotoxic effects. Further studies to evaluate this hypothesis will be important for understanding the fate of fatty acid species within the cell and potentially to assist in identifying targets for cellular rescues. One such study might investigate the potential for unsaturated fatty acids to serve as preferential ligands for the peroxisome proliferator-activated receptor family, which is known to modulate fatty acid uptake and oxidation.

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In summary, fatty acids are not only essential as sources of substrate for energy production, but individual fatty acids serve as signaling molecules for the induction of multiple different pathways for cellular function. Understanding the differential effects of specific lipid species on these downstream pathways is critical for understanding the basis of cellular lipotoxicity and, in turn, the pathogenesis of organ dysfunction in diseases such as diabetes. The data from Lockridge et al. (5) have provided important new insights into the effects of saturated and unsaturated fatty acids in mature cardiac myocytes at the level of gene expression. Additional studies to confirm the actual effect on cellular function will be important. Such studies might include evaluation of fatty acid oxidation rates, measurement of reactive oxygen species, and evaluation of ER and mitochondrial integrity after exposure to different fatty acids. In the long term, rescue strategies aimed at overexpression of specific gene targets that appear more cardioprotective or knockdown of those that are cardiotoxic may help guide potential therapies.

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