

Adipose tissue de novo lipogenesis

Unanticipated benefits in health and disease

BY MARK A. HERMAN AND BARBARA B. KAHN

Fatty acids are essential macromolecular cellular constituents serving critical structural and energetic roles. Synthesis of fatty acids endogenously (known as de novo lipogenesis, or DNL, Fig. 1) is traditionally thought to serve the purpose of converting excess carbohydrates into lipids for storage, because lipid is much more energy-dense than carbohydrate and is therefore a more efficient storage form. It is increasingly clear that fatty acids and

their derivatives are also important signaling molecules that affect many fundamental physiologic processes. DNL may produce lipid species with bioactivities distinct from those of lipids derived predominantly from the diet (1). Therefore, there is growing interest in the physiological role of DNL in normal biology and in disease states such as obesity, Type 2 diabetes and cardiovascular disease.

The two central enzymes of DNL, acetyl-CoA carboxylase and fatty acid synthase, use acetyl-CoA and malonyl-CoA derived from glucose or

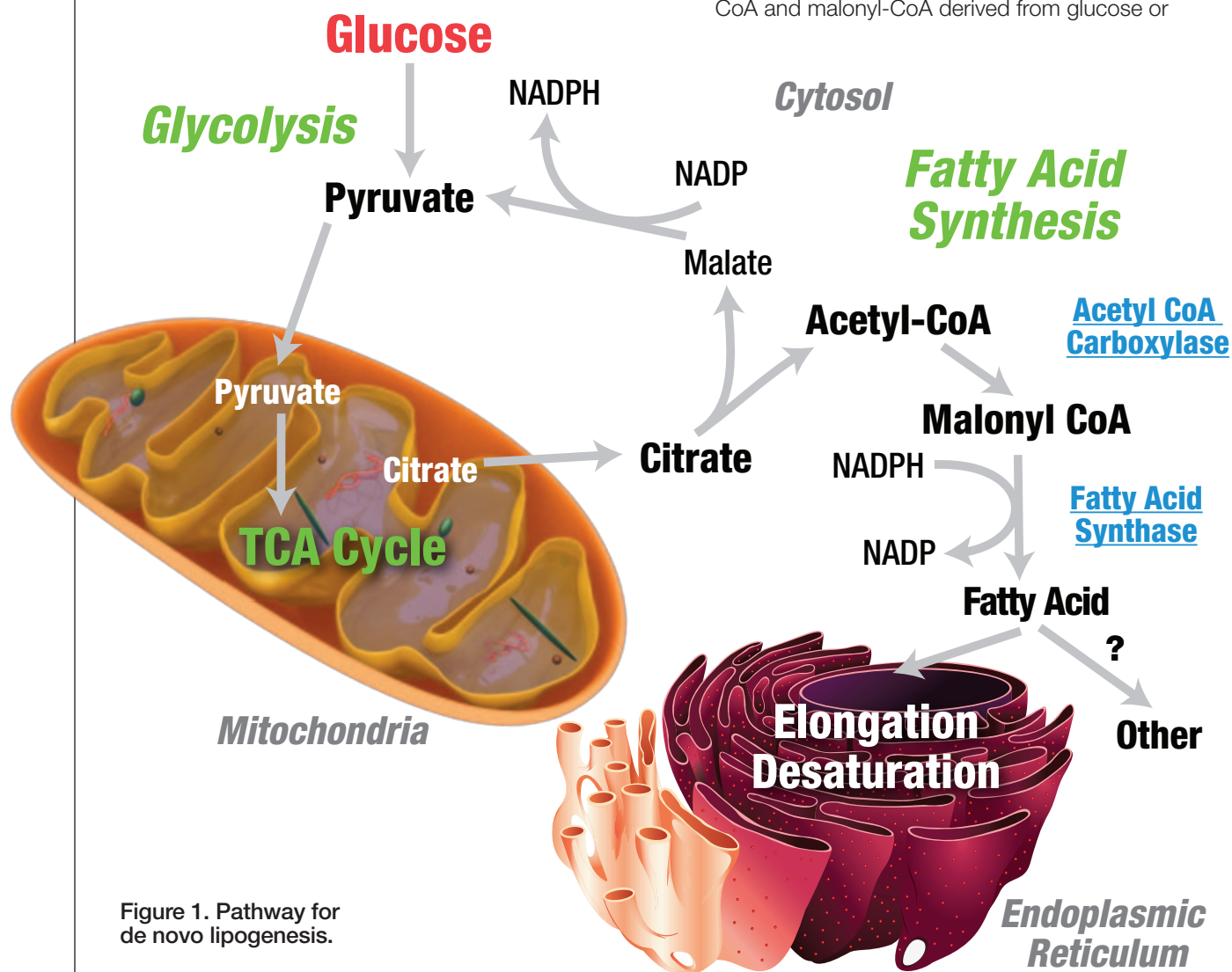


Figure 1. Pathway for de novo lipogenesis.

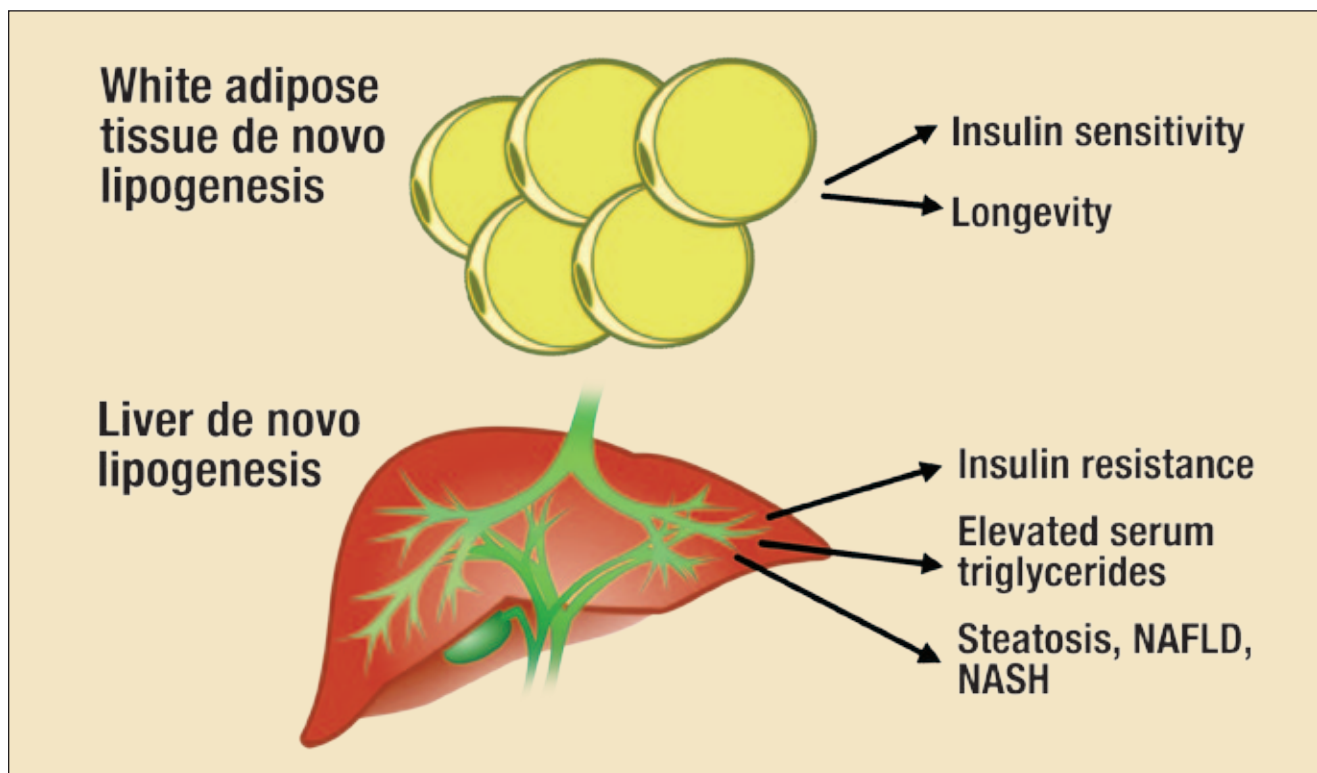


Figure 2. Divergent consequences of de novo lipogenesis (DNL) in adipose tissue compared to liver. NAFLD, nonalcoholic fatty liver disease. NASH, nonalcoholic steatohepatitis.

other carbon precursors to generate palmitate (Fig. 1). While palmitate may have detrimental effects, including enhancing production of proinflammatory cytokines and reactive oxygen species, other fatty acids have beneficial effects on metabolism, the immune system and cardiac function. For example, omega-3 fatty acids, though not synthesized endogenously, are used therapeutically to prevent complications of lipotoxicity in multiple tissues. Palmitate synthesized by DNL as well as dietary lipids can be modified by endogenous elongase and desaturase enzymes to produce multiple lipid species (Fig. 1). Many elongase and desaturase enzymes are coordinately regulated with other DNL enzymes (2). Thus, depending on the complement of enzymes in a specific tissue, the pattern of fatty acids produced by DNL may vary, and distinct fatty acids have very different biological properties.

In animals and humans, fatty acids are predominantly stored in adipose tissue as triglyceride. Most fatty acids in adipose tissue are obtained from dietary fat. Evolutionarily, the ability to store lipid conferred an advantage, because organisms that efficiently stored energy survived when food was scarce. Now, this propensity for storage

contributes to the growing obesity epidemic and its associated comorbidities. Interestingly, when surplus food is available, excess carbohydrate generally is oxidized rather than converted to fatty acids by DNL (3). The oxidation of excess dietary carbohydrate in preference to dietary fat is energetically efficient (i.e., it consumes less ATP than converting the excess carbohydrate into lipid) but this energy efficiency may exacerbate the propensity for obesity when food is plentiful. In conjunction with increased carbohydrate oxidation during high-carbohydrate/high-fat feeding, conversion of carbohydrate to fatty acids is decreased by downregulation of DNL in adipose tissue (4). Understanding the cellular mechanisms by which high-fat intake downregulates DNL in adipose tissue could provide new insights into the pathogenesis of obesity and diabetes.

The absence of a simple correlation between carbohydrate ingestion and the quantity of DNL in humans supports the concept that DNL may serve physiological functions aside from its role in the macronutrient energy economy. While most cells perform DNL, liver cells and adipocytes are particularly well adapted. DNL in liver has detrimental effects, including elevating serum triglycerides

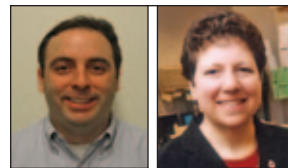
and increasing intrahepatic lipid (steatosis), leading to nonalcoholic fatty liver disease and steatohepatitis (Fig. 2) (5). In addition, elevated hepatic DNL strongly correlates with insulin resistance (6). In contrast, increased lipogenic enzyme expression in adipose tissue is associated with enhanced insulin sensitivity in humans (Fig. 2) independent of obesity (7).

DNL is driven by two master transcriptional regulators that are widely expressed – Sterol Response Element Binding Protein 1c and Carbohydrate Response Element Binding Protein. Both regulate expression of key lipogenic genes, such as fatty-acid synthase, acetyl-CoA carboxylase and ATP-citrate lyase (Fig. 1) (5). Insulin stimulates SREBP1c expression in the liver, and this is pronounced in hyperinsulinemic states such as Type 2 diabetes. In contrast, glucose and other carbohydrates regulate ChREBP activity. Expression of both DNL transcriptional regulators is elevated in liver in insulin-resistant states such as obesity. Knockdown of ChREBP in the livers of genetically obese ob/ob mice markedly improves insulin resistance and hepatic steatosis (8). In contrast, induction of ChREBP in adipocytes confers insulin sensitivity (4). Data suggest that adipose ChREBP may be involved in regulating whole-body insulin action and that ChREBP-driven DNL in adipocytes has beneficial metabolic effects (4) unlike the adverse effects of increased DNL in liver cells. SREBP1c appears to be a dominant regulator of DNL in liver but not adipose tissue, because SREBP1c knockout reduces hepatic but not adipose DNL enzyme expression (9). Hence, ChREBP is the dominant regulator of DNL in adipose tissue (4).

Investigation of the molecular mechanisms regulating DNL in liver and adipose tissue also supports the view that adipose DNL, unlike hepatic DNL, may be metabolically beneficial. Liver-specific deletion of SCAP, a protein required for cleavage of SREBP1c to its active form, reduces hepatic DNL (10). This is accompanied by a compensatory four-fold increase in adipose DNL associated with improved fasting glycemia, glucose tolerance and insulin sensitivity. In addition, genetically deleting adipose tissue lipid chaperones aP2 and mal1 increases adipose DNL and renders mice resistant to diet-induced obesity, fatty liver disease, insulin resistance and Type 2 diabetes (1). The improved metabolic phenotype has been attributed to insulin-sensitizing properties of palmitoleate, a potentially beneficial fatty-acid species produced at increased rates as a result of increased adipose DNL (1). These genetic studies causally link increased adipose DNL with beneficial effects on whole-body metabolism.

Additional recent observations support the possibility that adipose DNL may serve unanticipated beneficial physiological functions. Calorie restriction prolongs life span in numerous mammalian species and delays the development of aging-associated diseases such as diabetes and atherosclerosis (11). The mechanism is unknown. From an efficiency perspective, one might expect calorie restriction to reduce DNL, which is a wasteful energetic process. However, the opposite is observed. Calorie-restricted mice demonstrate a four-fold increase in adipose tissue DNL (12). It is not known whether this mediates the therapeutic effects of calorie restriction. But it is highly plausible that it mediates favorable metabolic effects, because enhanced DNL in adipose tissue confers improved glucose homeostasis (4).

Thus, growing evidence suggests that increasing adipose tissue DNL may provide beneficial health effects in contrast with the effects of DNL in liver tissue. Strategies to enhance DNL specifically in adipose tissue and to identify and administer salutary bioactive lipids may provide new therapies for metabolic and cardiovascular disease. XXXX



Mark A. Herman (mherman1@bidmc.harvard.edu) is an instructor of medicine at Harvard Medical School and a faculty member in the Division

of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical Center. Barbara B. Kahn (bkahn@bidmc.harvard.edu) is the George R. Minot professor of medicine at Harvard Medical School, vice chair for Research Strategy in the department of medicine, and former chief of the Division of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical Center.

REFERENCES

1. Cao, H., et al. (2008) *Cell*. **134**:933–944.
2. Wang, Y., et al. (2006) *Journal of Lipid Research*. **47**:2028–2041.
3. McDevitt, R.M., et al. (2001) *The American Journal of Clinical Nutrition*. **74**:737–746.
4. Herman, M.A., Peroni, O.D., Kahn, Barbara B. (2009) *Diabetes*. **58**: suppl. 1, A351.
5. Postic, C. and Girard, J. (2008) *J. Clin. Invest.* **118**:829–838.
6. Hudgins, L.C., Parker, T.S., Levine, D.M., Hellerstein, M.K. (2011) *Journal of Clinical Endocrinology & Metabolism*. **96**:861–868.
7. Roberts, R., et al. (2009) *Diabetologia*. **52**:882–890.
8. Dentin, R. (2006) *Diabetes*. **55**:2159–2170.
9. Shimano, H., et al. (1997) *J. Clin. Invest.* **100**:2115–2124.
10. Kuriyama, H., et al. (2005) *Cell Metabolism* **1**:41–51.
11. Heilbronn, L.K., Ravussin, E. (2003) *The American Journal of Clinical Nutrition*. **78**:361–369.
12. Bruss, M.D., Khambatta, C.F., Ruby, M.A., Aggarwal, I., Hellerstein, M.K. (2010) *American Journal of Physiology — Endocrinology and Metabolism*. **298**:E108–E116.