See corresponding article on page 737.

No common energy currency: de novo lipogenesis as the road less traveled[1,2]

Marc K Hellerstein

Bees make wax (lipid) from honey (carbohydrate). Pigs fatten on a grain diet. Indeed, all organisms, from bacteria to mammals, have the enzymes of de novo lipogenesis. The physiologic function of de novo lipogenesis has therefore seemed obvious to biochemists: the de novo lipogenesis pathway links carbohydrates and fats, the 2 most important forms of chemical energy for most organisms.

Because storage of energy as lipid is much more efficient than storage as carbohydrate, the presumption has been that animals use de novo lipogenesis as a metabolic safety valve for storage of carbohydrate energy present in excess of carbohydrate oxidative needs (ie, carbohydrate energy surplus). On the basis of this presumed role, inhibitors of de novo lipogenesis [such as (–)hydroxycitrate, an inhibitor of ATP citrate (*pro-S*)-lyase] have received attention as potential therapeutic agents for obesity and hyperlipidemia.

Most experimental data in humans, however, contradict this view of the function of de novo lipogenesis. Initial studies in which indirect calorimetry was used showed little or no net de novo lipogenesis after short-term carbohydrate overfeeding (1). Subsequent isotopic studies confirmed the absence of quantitatively significant flux through hepatic de novo lipogenesis under most conditions of carbohydrate energy surplus (2, 3).

In this issue of the Journal, McDevitt et al (4) contribute useful data relevant to this topic. In a well-designed study, these investigators combined whole-body room indirect calorimetry (to measure net fuel oxidation and de novo lipogenesis) with isotopic measurement of hepatic de novo lipogenesis (by isotope incorporation from deuterated water into triacylglycerol of circulating VLDL). McDevitt et al report that hepatic de novo lipogenesis was stimulated by 4 d of surplus carbohydrate energy in women, that this stimulation was not significantly different when the surplus carbohydrate was in the form of glucose or sucrose, and that the de novo lipogenesis values reached were similar for lean and obese women. Additionally, McDevitt et al report that, in all settings, the total de novo lipogenesis flux represented a small fraction of both the surplus carbohydrate energy ingested and the total fat stored in the body. The authors calculated that between 3 and 8 g fat/d was produced through de novo lipogenesis compared with 360–390 g carbohydrate ingested/d and 60–75 g body fat stored/d. Thus, the addition of excess carbohydrate energy to a mixed diet so that total energy intake exceeded total energy expenditure (TEE) increased body fat stores, but not by conversion of the carbohydrate to fat. Instead, the oxidation of dietary fat was suppressed and fat storage thereby increased.

Several points regarding the experimental design of McDevitt et al should be noted. First, the overfeeding protocol provided less total carbohydrate energy than daily TEE. It was therefore energetically possible to substitute carbohydrate for other fuels without changing TEE or breaking any laws of thermodynamics. The few exceptions to the rule that de novo lipogenesis is quantitatively minor have been when carbohydrate energy intake massively exceeds TEE, eg, the Guru Walla overfeeding tradition in Cameroon, wherein adolescent boys ingest > 29.3 MJ (7000 kcal) carbohydrate/d and gain 12 kg body fat over 10 wk while eating only 4 kg fat (5). Thus, de novo lipogenesis does become a quantitatively major pathway when carbohydrate energy intake exceeds TEE, but this circumstance is unusual in daily life.

Second, the period of overfeeding used by McDevitt et al (4) was relatively brief and included substantial dietary fat. Total body stores or proportions of different fatty acids would not have been altered by the 4-d protocol. If fatty acids themselves inhibit de novo lipogenesis, we cannot extrapolate the results to longer periods of surplus-carbohydrate, low-fat diets.

Third, the authors measured only hepatic, not adipose, de novo lipogenesis. Indeed, there is an element of tautology in the authors' argument that hepatic de novo lipogenesis is not quantitatively significant. McDevitt et al assumed a fixed VLDL-triacylglycerol production rate (30 g/d, or 300 $mg \cdot kg^{-1} \cdot d^{-1}$) on the basis of values published in the literature. Even if de novo lipogenesis were 100%, the maximum quantitative contribution would be 30 g/d (compared with a carbohydrate intake of 350 g/d). It would have been preferable to measure VLDL-triacylglycerol production rates directly under the conditions of overfeeding to exclude the possibility of VLDL-triacylglycerol production rates of 100 g/d, for example.

Some experimental evidence for a potential role of adipose de novo lipogenesis has emerged. Aarsland et al (6) administered glucose to human subjects at rates greatly above TEE. After 4–7 d of overfeeding, hepatic de novo lipogenesis (measured isotopically)

[1] From the Department of Nutritional Sciences & Toxicology, University of California, Berkeley, and the Department of Medicine, San Francisco General Hospital, University of California, San Francisco.

[2] Address reprint requests to MK Hellerstein, Department of Nutritional Sciences, 119 Morgan Hall, University of California, Berkeley, CA 94720-3104. E-mail: march@nature.berkeley.edu.

was stimulated 10-fold above baseline values but remained <3% of whole-body net de novo lipogenesis according to indirect calorimetry. These authors concluded that adipose de novo lipogenesis must be occurring. Using very-long-term labeling protocols with ^2H_2O, we recently observed considerably more de novo lipogenesis in adipose tissue than in liver in rodents (S Turner, E Murphy, MK Hellerstein, unpublished observations, 2001). Studies in which adipose lipids of humans consuming euenergetic diets were labeled with ^2H_2O have not shown high rates of de novo lipogenesis (7; F Antelo, A Strawford, MK Hellerstein, unpublished observations, 2001), but these techniques have not yet been used under conditions of carbohydrate overfeeding. This is an area that needs further investigation.

Finally, technical factors are unlikely to explain the low rates of de novo lipogenesis reported by McDevitt et al. If anything, their method somewhat overestimates de novo lipogenesis because incorporation of deuterium into the glycerol moiety of triacylglycerol will result in an artifactual 6–7% de novo lipogenesis and elongation of fatty acids might add a further slight overestimation of de novo lipogenesis.

The model of the human macronutrient energy economy that emerges from the study of McDevitt et al is consistent with previous work (2, 3, 8, 9). In the hierarchy of fuels, dietary carbohydrate appears to have a higher priority for oxidation than does dietary fat; when both are present, carbohydrate is chosen. The 2 major macronutrient energy sources (carbohydrates and fats) are not, however, interconvertible energy currencies. Fat cannot be converted to carbohydrate in animals because animals lack the enzymes of the glyoxylate pathway, and carbohydrate is not converted to fat because of a functional block of uncertain cause.

What are the implications of this model? Some conclusions should not be drawn. First, these results do not mean that extra carbohydrate energy represents "free" energy in terms of body fatness. By sparing fat in the body's fuel mixture, surplus carbohydrate energy will make people fatter, even though it is not directly converted to fat. The absence of significant de novo lipogenesis is bad news for high-carbohydrate dieters for another reason, in that the high thermogenic cost of de novo lipogenesis cannot be invoked as an energy-dissipating feature of such diets. Second, the effects of carbohydrate-rich diets on macronutrient balances should not be confused with their potential effect on plasma lipids and atherogenesis. High-carbohydrate euenergetic or hyperenergetic diets consistently induce hypertriglyceridemia, the public health consequences of which remain controversial (10).

The implications of not having a single interconvertible energy currency, but instead having 2 independent, although interacting, macronutrient economies (8), remain intriguing and incompletely explored. Does the rule that carbohydrate availability to tissues controls whole-body fuel selection also apply to endogenous glucose production by the liver (9)? It might then be concluded that hepatic metabolism and hepatic genes are more likely to contribute to obesity through effects on glucose production than through effects on fat synthesis (11). Also, are there regulatory, as opposed to quantitative, functions of the de novo lipogenesis pathway? Certainly, malonyl-CoA, the first committed metabolite in the de novo lipogenesis pathway, has several known regulatory actions. In addition to well-established antiketogenic actions in liver, malonyl-CoA concentrations are believed to influence fuel selection in muscle, fuel sensing and insulin secretion in the pancreatic β cell, and perhaps fuel sensing and appetite regulation by the brain (12). The fate of tissue malonyl-CoA generated for regulatory functions is a related, unanswered question (eg, is disposal of regulatory malonyl-CoA an unrecognized function of the de novo lipogenesis pathway?).

Finally, what is the role of de novo lipogenesis in human disease? Recent studies (13) have identified different insulin signaling pathways for de novo lipogenesis and cholesterol synthesis, on the one hand, and carbohydrate metabolism, on the other, as well as co-induction of de novo lipogenesis with cholesterogenesis by overexpression of the sterol response element binding protein. Thus, is de novo lipogenesis involved in the pathogenesis of insulin resistance or hypercholesterolemic syndromes? Or does de novo lipogenesis influence intracellular signaling pathways involving myristoylation, palmitoylation, or membrane fatty acids? These questions and more arise from the observation that de novo lipogenesis is the pathway of last resort and that, at least regarding converting carbohydrates to fats, humans are neither bees nor pigs.

REFERENCES

1. Acheson KJ, Flatt JP, Jequier E. Glycogen synthesis versus lipogenesis after a 500 gram carbohydrate meal in man. Metabolism 1982;31:1234–40.
2. Hellerstein MK, Schwarz JM, Neese RA. Regulation of hepatic de novo lipogenesis in humans. Annu Rev Nutr 1996;16:523–57.
3. Hellerstein MK. De novo lipogenesis in humans: metabolic and regulatory aspects. In: Proceedings of FAO/IDECG Workshop, Lower and Upper Limits of Adaptation to Energy Intake and its Principal Substrates, Carbohydrates and Lipids. Eur J Clin Nutr 1999;53:S53–65.
4. McDevitt RM, Bott SJ, Harding M, Coward WA, Bluck LJ, Prentice AM. De novo lipogenesis during controlled overfeeding with sucrose or glucose in lean and obese women. Am J Clin Nutr 2001;74:737–46.
5. Pasquet P, Brigant L, Froment A, et al. Massive overfeeding and energy balance in men: the Guru Walla model. Am J Clin Nutr 1992;56:483–90.
6. Aarsland A, Chinkes D, Wolfe RR. Contributions of de novo synthesis of fatty acids to total VLDL-triglyceride secretion during prolonged hyperglycemia/hyperinsulinemia in normal man. J Clin Invest 1996;98:2008–17.
7. Guo ZK, Cella LK, Baum C, Ravussin E, Schoeller DA. De novo lipogenesis in adipose tissue of lean and obese women: application of deuterated water and isotope ratio mass spectrometry. Int J Obes 2000;24:932–7.
8. Flatt JP. Dietary fat, carbohydrate balance, and weight maintenance: effects of exercise. Am J Clin Nutr 1987;45:296–306.
9. Schwarz JM, Neese RA, Turner S, Dare D, Hellerstein MK. Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. J Clin Invest 1995;96:2735–43.
10. Parks EJ, Hellerstein MK. Effects of low-fat, high carbohydrate diets on serum lipids in humans: a review of the literature. Am J Clin Nutr 2000;71:412–33.
11. Pagliassotti MJ, Horton TJ, Gayles EC, Koppenhafer TA, Rosenzweig TD, Hill JO. Reduced insulin suppression of glucose appearance is related to susceptibility to dietary obesity in rats. Am J Physiol 1997;272:R1264–70.
12. Ruderman NB, Saha AK, Vavvas D, Witters L. Malonyl-CoA, fuel sensing, and insulin resistance. Am J Physiol 1999;276:E1–18.
13. Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein DL. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. Mol Cell 2000;6:77–86.