Fructose and dietary thermogenesis[1,2]

Luc Tappy and Eric Jéquier

ABSTRACT Ingestion of nutrients increases energy expenditure above basal metabolic rate. Thermogenesis of carbohydrate comprises two distinct components: an obligatory component, which corresponds to the energy cost of carbohydrate absorption, processing, and storage; and a facultative component, which appears to be related with a carbohydrate-induced stimulation of the sympathetic nervous system, and can be inhibited by β-adrenergic antagonists. Fructose ingestion induces a greater thermogenesis than does glucose. This can be explained by the hydrolysis of 3.5–4.5 mol ATP/mol fructose stored as glycogen, vs 2.5 mol ATP/mol glucose stored. Therefore the large thermogenesis of fructose corresponds essentially to an increase in obligatory thermogenesis. Obese individuals and obese patients with non-insulin-dependent diabetes mellitus commonly have a decrease in glucose-induced thermogenesis. These individuals in contrast display a normal thermogenesis after ingestion of fructose. This may be explained by the fact that the initial hepatic fructose metabolism is independent of insulin. This observation indicates that insulin resistance is likely to play an important role in the decreased glucose-induced thermogenesis of these individuals. *Am J Clin Nutr* 1993;58(suppl):766S–770S.

KEY WORDS Thermogenesis, obesity, non-insulin-dependent diabetes, weight loss

Introduction

Since the beginning of the century it has been observed that the energy expenditure of humans and animals increases significantly after ingestion of a meal. This increase in energy expenditure has first been attributed to the intake of protein, and was termed specific dynamic action (of protein). It was subsequently recognized that not only protein ingestion, but also ingestion of carbohydrate and, to a lesser extent, of fat, increases significantly the energy expenditure. This dietary-induced thermogenesis is accounted for by the energy cost of nutrient absorption, handling, and storage. Dietary-induced thermogenesis is now recognized to be a component of total energy expenditure and represents $\approx$ 10% of 24-h energy expenditure in normal sedentary humans.

After ingestion of a meal, a certain amount of ATP is expended in the processes of intestinal absorption and nutrient storage. These processes result in an obligatory thermogenic response, ie, an increase in resting energy expenditure above basal metabolic rate. The nutrient-induced thermogenesis can be assessed from the ratio of the number of ATP molecules used in the processes of nutrient absorption and storage to the number of ATP molecules synthesized through the complete nutrient oxidation (1).

Thermogenesis of glucose and carbohydrate

Ingested glucose is absorbed in the duodenum by an energy-requiring process in which $\approx$ 0.5 mol ATP/mol glucose is hydrolyzed. Subsequently, absorbed glucose can either be oxidized to carbon dioxide and water, or can be stored nonoxidatively as glycogen; another metabolic pathway that occurs in the liver is conversion of glucose into fatty acids in the process of lipogenesis. This latter process has however been shown to be quantitatively of little importance in humans unless there is marked carbohydrate and energy overfeeding (2, 3).

The initial metabolism of 1 mol glucose requires consumption of 2 mol ATP, one for the phosphorylation to glucose-6-phosphate and one for the phosphorylation to fructose-1,6-diphosphate. Complete oxidation of fructose-1,6-diphosphate releases a total of 38 mol ATP. The net gain of ATP per mole of exogenous glucose oxidized is therefore $38-2 = 36$ mol ATP. Endogenous glucose derives from glycogen stores and glycogenolysis yields glucose-6-phosphate; the latter is subsequently phosphorylated to fructose-1,6-diphosphate, with the hydrolysis of only 1 mol ATP/mol (vs 2 mol for exogenous glucose). Oxidation of 1 mol glycosyl residue from endogenous glycogen therefore yields a net gain of 37 mol ATP vs 36 mol for endogenous glucose. This slight difference accounts for a glucose-induced thermogenesis of $\approx$ 2–3% (or 1/36) during oxidation of exogenous glucose.

Glucose storage as glycogen is a process in which consumption of 2 mol ATP/mol are required for phosphorylation to glucose-6-phosphate and for regeneration of uridine triphosphate (UTP) after uridyl diphosphoglucose synthesis. In comparison with the 38 mol ATP produced on complete oxidation of glucose, the energy cost of glucose storage as glycogen thus corresponds to $\approx$ 5% (or 2/38) of the energy content of intravenous glucose stored or to $\approx$ 7% (or 2.5/38) of the energy content of oral glucose stored. Cycling of glucose to glucose-6-phosphate and back to glucose, to fructose-1,6-diphosphate and back to glucose-6-phosphate, or to lactate and back to glucose is constantly occurring at variable rates in humans. These substrate cycles are energy-requiring processes, which add to the aforementioned values of glucose-induced thermogenesis. The amount of energy expended in these cycles represents only a small portion of total energy expenditure even in clinical situations (eg, extended burn, hyperthyroidism) where their activity is increased (4, 5).

[1] From the Institute of Physiology, University of Lausanne, Lausanne, Switzerland.

[2] Address reprint requests to L Tappy, Institut de physiologie, 7, rue du Bugnon, 1005 Lausanne, Switzerland.

Am J Clin Nutr 1993;58(suppl):766S–70S. Printed in USA.

Experimentally, the values of the thermogenesis of oral glucose represent ≈8% of the energy content of the glucose ingested (6). Values in the same range are reported during glucose and insulin infusion at euglycemia (7, 8). During glucose and insulin infusion at euglycemia, the thermogenesis of infused glucose is correlated with the amount of glucose stored as glycogen (8). The thermogenesis per gram glucose stored amounts to ≈12% of its energy content and thus exceeds significantly the calculated value of 5% for direct storage of intravenous glucose to glycogen (8). This observation indicates that some extent of substrate cycling (indirect pathway of glycogen formation from lactate, or substrate cycles, as discussed above) takes place.

Fatty acids synthesis from glucose (lipogenesis) is a process with a high energy requirement that would produce a thermogenesis amounting to ≈26% of the energy content of glucose (1). This process is however quantitatively much less important than is glucose storage as glycogen in human subjects (2, 3).

Interestingly, β adrenergic blockade decreases the glucose-induced thermogenesis during glucose and insulin infusion (9). Under these conditions, the thermogenesis expressed per gram glucose stored becomes very close to the theoretical value of 5%. Infusion of glucose + insulin induces a stimulation of the sympathetic nervous system by yet unspecified mechanisms (10–12). The decrease in glucose-induced thermogenesis after β adrenergic blockade suggests that stimulation of the sympathetic nervous system may activate substrate cycling in which extra energy is expended. It has indeed been reported that epinephrine increases the rate of cycling of glucose to lactate and back to glucose, or Cori cycle (13), a process in which two molecules of ATP are consumed during each cycle.

Parasympathetic nervous system blockade by atropine suppresses markedly the thermogenesis after oral glucose or after ingestion of a mixed meal, but leaves the thermogenesis to intravenous glucose unaffected (14–16). This effect of parasympathetic nervous system blockade on meal-induced thermogenesis is likely to be explained by a decrease in the gastric emptying rate.

Thermogenesis of proteins

It has been estimated, by using respiratory carbon dioxide and oxygen exchange monitoring and measurement of nitrogen excretion rate, that protein ingestion increases energy expenditure by an amount corresponding to 20–35% of its energy content (17). Similarly, the thermogenesis of infused amino acids amounts to ≈20% of their energy content (18). Ingested proteins are degraded in the gut into amino acids, a process that does not require energy consumption. Like glucose, amino acids are absorbed by an energy-requiring process in which 0.5 mol ATP are consumed for each mole of amino acids absorbed. After absorption, amino acids have two major metabolic fates. On one hand, they can be deaminated, their amino group transferred to urea in the liver, and their carbon skeleton converted to glucose in the process of gluconeogenesis. When the newly synthesized glucose is oxidized to carbon dioxide and water, it can be calculated that this indirect process of amino acid oxidation requires the consumption of an amount of energy representing ≈25% of the energy content of amino acids. The other pathway of amino acid metabolism is protein synthesis. In this process, energy is expended for the formation of amino-acyl tRNA and in the synthesis of the peptide bounds, the total energy consumed can be calculated to also be ≈25% of the energy content of amino acids. Therefore, calculated thermogenesis of amino acids represents 25% of their energy content, irrespective of the metabolic pathway followed (1). This theoretical value is close to the measured values of ingested protein or of infused amino acids.

Thermogenesis of fat

Of the three major nutrients, fat is the substrate that least stimulates energy expenditure. An increase in energy expenditure corresponding to ≈2% of the fat energy content has been reported during infusion of an emulsion of triglyceride (19). This slight stimulation of energy expenditure can be accounted for by ATP consumption in the process of free fatty acid reesterification to triglyceride.

Fructose as a metabolic substrate

Fructose is a sugar naturally present in fruit and honey. Sucrose or refined sugar is constituted by the condensation of one molecule of glucose and one of fructose, and is cleaved in the intestinal lumen into simple sugars by the action of intestinal α-hydrolase. It is currently estimated that fructose may contribute as much as 10–15% of the total dietary carbohydrate intake in Westernized countries. Oral fructose is metabolized essentially in the liver, where the enzyme fructokinase catalyzes its rapid phosphorylation into fructose-1-phosphate. The removal of fructose from the circulation is very rapid and efficient, with the consequence that the concentration of this substrate in the systemic circulation does not exceed 1 mmol/L after ingestion of even large doses of fructose.

The enzyme hexokinase present in muscle and adipose cells is also able to phosphorylate fructose to fructose-6-phosphate. The affinity of hexokinase for fructose is however severalfold lower than for glucose, and therefore metabolism of fructose by hexokinase is unlikely to be significant after oral fructose when physiological blood glucose concentrations are present (20–23). Even after intravenous infusion of fructose that induces a plasma fructose concentration comparable to that of glucose, the ratio of fructose to glucose metabolized by this pathway remains low. In contrast, the transport of fructose into liver cells is rapid and independent of the action of insulin. Its phosphorylation to fructose-1-phosphate by fructokinase is not regulated by insulin. Fructose-1-phosphate is then converted to glyceraldehyde phosphate (GAP) and dihydroxyacetone phosphate (DHAP) by the enzyme aldolase B.

Dihydroxyacetone phosphate can be further degraded to pyruvate and enter the tricarboxylic acid cycle, or can be reconverted into glucose in the process of gluconeogenesis. Glyceraldehyde is essentially converted to α glyceraldehyde phosphate, and from there follows the same fate as DHAP (oxidation or gluconeogenesis) (20, 21). The whole process of fructose metabolism does not depend on the presence of insulin. It has indeed been shown in normal humans that fructose metabolism is unaffected by somatostatin-induced insulinopenia (24).

After administration of large doses of oral fructose, the substrate is efficiently removed from the portal circulation, and thus metabolized essentially by the liver. Under these circumstances the amount of fructose metabolized in the liver exceeds the he-

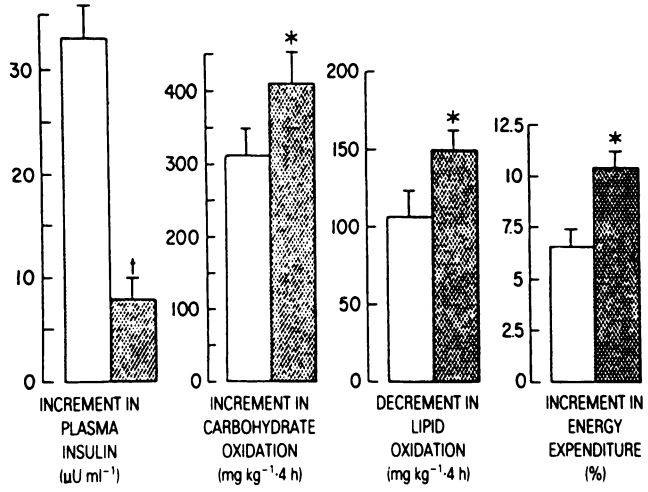

FIG 1. Increments in plasma insulin concentration, carbohydrate oxidation, and energy expenditure and decrement in lipid oxidation during the 4 h after ingestion of 75 g glucose (□) or fructose (■) in lean human subjects. (Reproduced from reference 25, with permission); to convert from μU/mL to pmol/L, multiply by 7.175.)

patic oxidation capacity, with the consequence that fructose has to be disposed of nonoxidatively in large part. Plasma lactate concentrations are increased by fructose ingestion, suggesting that part of the fructose administered is liberated into the systemic circulation as lactate (25); the latter may be metabolized in peripheral tissues or be converted to glucose and stored as glycogen in liver or in skeletal muscle. Based on renal and hepatic catheterization studies during systemic infusion of fructose in humans, it has been estimated that ≈20% of fructose is recirculated as lactate (26). Fructose is also reconverted directly into glucose in the liver and can be stored as glycogen (27). In vitro studies have corroborated that fructose is a potent gluconeogenic precursor and that substantial amounts of [^{14}C]glycogen are obtained when liver cells are incubated with [^{14}C]fructose (28). Finally, fructose may be converted into fatty acids by lipogenesis in liver cells. The importance of this pathway has not been specifically determined. Calorimetric studies however suggest that it is unlikely to be a major pathway of fructose disposal, because respiratory quotients greatly exceeding 1.0 have not been observed after oral fructose (25).

Thermogenesis of oral and intravenous fructose

Ingestion of an oral load of fructose elicits a greater increase in energy expenditure than does a similar load of glucose (25) (**Fig 1**). The increase in energy expenditure is also greater after ingestion of equivalent loads of either equimolar mixtures of fructose and glucose or of sucrose compared with glucose alone (29). A greater thermic effect of fructose is also observed when fructose or glucose are administered as part of a mixed meal (30). Several mechanisms explain the large stimulation of energy expenditure after fructose. Intestinal absorption of fructose requires consumption of 0.5 mol ATP/mol as for glucose. As discussed above, fructose is rapidly metabolized in the liver because of the high activity of the enzyme fructokinase and because its degradation bypasses the regulatory steps of glycolysis (hexokinase/glucokinase and phosphofructokinase). This degradation however surpasses the oxidative capacity of the liver. As a result, a large part of fructose is disposed of nonoxidatively as glycogen deposition in the liver or muscle (27, 31). However, compared with glucose, fructose has first to be converted to triose-phosphates by the enzyme aldolase B and reconverted to glucose in the gluconeogenic pathway. This conversion requires 1 mol ATP for synthesis of fructose-1-phosphate and 1 mol ATP for conversion of glyceraldehyde to GAP.

DHAP and GAP are converted to glucose-6-phosphate without ATP consumption. Glucose-6-phosphate will then be converted to glucose-1-phosphate and to uridyl diphosphoglucose before being deposited as glycogen, and 1 mol ATP will be required for UTP regeneration. Thus, storage of oral fructose as glycogen will require 3.5 mol ATP/mol compared with 2.5 mol with oral glucose, resulting in an obligatory energy cost of storing fructose of ≈9% of its energy content (**Fig 2**). It may even be considerably more elevated if triose-phosphates are first converted into pyruvate and lactate before gluconeogenesis. Interestingly, it was observed that stimulation of carbohydrate oxidation is greater after oral fructose than after oral glucose (25) (Fig 1). Nonoxidative glucose disposal may therefore appear to be lower after fructose. This may however not be so, because hepatic glucose production was unchanged after intravenous fructose (32) (and presumably after oral fructose as well), whereas it is significantly suppressed after glucose. Endogenous glucose production was even slightly increased after intravenous fructose, consistent with a stimulation of gluconeogenesis. Thus, ongoing gluconeogenesis and the higher cost of glycogen deposition are likely mechanisms to account for the greater thermogenesis after fructose than after glucose ingestion.

Fructose ingestion leads to a greater increase in the respiratory quotient than does glucose ingestion (25, 30). This may be due to the more rapid removal and metabolism of fructose by the liver. It may also indicate that part of the fructose metabolized is converted to fatty acids in the process of lipogenesis. Fructose conversion into fatty acids is a metabolic pathway that proceeds with a respiratory quotient markedly higher than one, and would lead to consumption of ≈26% of the energy content of fructose (1). The observation of respiratory quotient transiently exceeding 1.0 after oral fructose is consistent with some extent of lipogenesis (25). However, the measured increase in energy expenditure of ≈10% after fructose is not consistent with lipogenesis

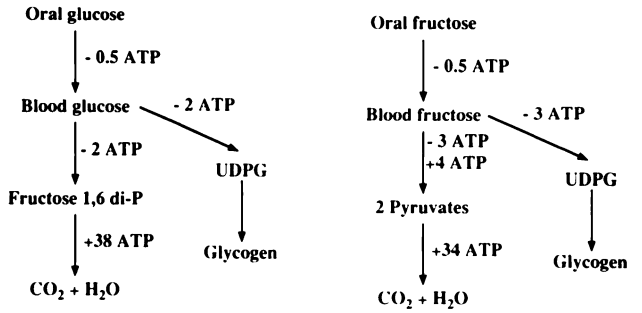

FIG 2. Summary of adenosine triphosphate (ATP) hydrolyzed in the initial steps of metabolism and synthesized during complete oxidation for oral glucose or fructose [assumption: fructose-6-P → dihydroxyacetone phosphate (DHAP) + glyceraldehyde phosphate (GAP) → glucose-6-phosphate]. The thermic effect of these sugars can be estimated theoretically from the ratio of ATP hydrolyzed to ATP synthesized). P, phosphate; UDPG, uridyldiphosphoglucose.

being an important pathway for nonoxidative fructose disposal. Because fructose cannot be stored as such, a larger part of nonoxidative fructose disposal has, therefore, to be glycogen deposition.

Interestingly, the thermogenesis after oral or intravenous fructose is suppressed by 40% after the administration of β adrenergic agents (25, 33), without affecting the amount of carbohydrate oxidized or the nonoxidative fructose disposal. This observation indicates that fructose administration, like glucose, activates β adrenergic–sensitive substrate cycles.

Glucose- and fructose-induced thermogenesis in insulin-resistant states

Obese individuals with impaired glucose tolerance and obese patients with non-insulin-dependent diabetes mellitus (NIDDM) have an impaired stimulation of energy expenditure after oral glucose administration or during insulin/glucose infusion in euglycemic clamp experiments, in which blood glucose concentrations are maintained constant while insulin is infused. This impairment of glucose-induced thermogenesis is related to a decrease in nonoxidative glucose disposal, presumably as glycogen. A decrease in insulin-mediated glucose storage as glycogen in skeletal muscle during euglycemic clamp experiments is a prominent feature of insulin-resistant NIDDM patients (for review, *see* ref 34). When individuals with normal insulin sensitivity and obese insulin-resistant patients are studied during euglycemic hyperinsulinemic clamps experiments at different degrees of insulinemia to provide comparable data an total glucose metabolism in both groups, a similar thermic effect of infused glucose is observed (35). This finding confirms that the impairment of the glucose-induced thermogenesis is secondary to insulin resistance in obese patients.

Although oral glucose elicits lower thermogenesis in obese patients with impaired glucose tolerance and obese patients with NIDDM than in lean control subjects, it was observed that after similar doses of oral fructose, thermogenesis was normalized in all groups of patients (36) (**Fig 3**). Net carbohydrate (ie, fructose + glucose) oxidation was also improved although it was not normalized. This can be explained by the fact that fructose is metabolized, for its first steps at least, independently of insulin, and removed from the portal circulation as efficiently in obese and NIDDM patients as in lean control subjects. As a result, nonoxidative storage of fructose is normal in these patients compared with the impaired nonoxidative glucose disposal after an oral glucose load.

Conclusion

The greater thermic effect of fructose, its nondependence on insulin for its metabolism, and its greater sweetening potency compared with glucose are factors that may speak in favor of fructose as a valuable carbohydrate for the dietary management of obesity and NIDDM. This enthusiasm must, however, be tempered by the observations in animals and humans that chronic fructose or sucrose feeding has been reported to induce insulin resistance, hyperlipemia, and hypertension (37, 38). [*See* discussion of fructose and hyperlipidemia (39) and diabetes mellitus (40)]. It has been reported that consumption of diets enriched with sucrose over several weeks reduced insulin sensitivity in

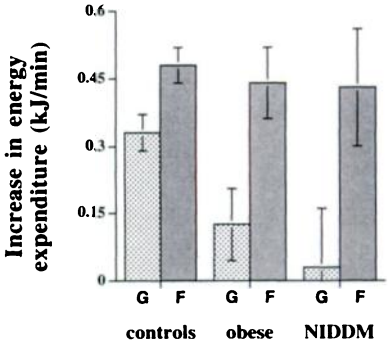

FIG 3. Increase in energy expenditure during the 4 h after ingestion of 75 g of either glucose (G) or fructose (F) in lean humans (control subjects), obese nondiabetic patients, and obese patients with non-insulin-dependent diabetes mellitus (NIDDM). (From reference 36, with permission).

normal human subjects (41). Similar observations have been made in rats chronically fed with sucrose or fructose (42). In addition, high fructose feeding was observed to induce hypertension in rats. This increase in blood pressure was attributed to fructose-induced insulin resistance and hyperinsulinemia because it could be prevented by administration of somatostatin (43, 44). On the other hand, several recent studies in patients with NIDDM showed that chronic fructose feeding lowered mean plasma glucose and decreased glucosuria (45, 46). In regard to weight control, it has also been shown in rats and in men that hypoenergetic diets containing sucrose (half of which is fructose) lead to a lesser weight loss than diets containing partial hydrolysate of starch; this difference was, however, not apparent in women; the mechanisms involved have not been elucidated (47–49).

Thus, further studies are clearly needed to determine the metabolic alterations that may take place during chronic fructose or sucrose feeding. Because hyperinsulinemia may constitute an important risk factor for cardiovascular diseases, it appears important that the effects of feeding high-fructose diets over prolonged periods of time on insulin sensitivity be directly assessed by specific techniques such as euglycemic hyperinsulinemic clamp experiments. The effects of fructose feeding on blood pressure control in humans requires further investigation.

References

1. Flatt JP. The biochemistry of energy expenditure. In: Bray GA, ed. Recent advances in obesity research II. London: Newman, 1978: 211–8.
2. Acheson KJ, Flatt JP, Jéquier E. Glycogen synthesis versus lipogenesis after a 500 gram carbohydrate meal in man. Metabolism 1982;31:1234–40.
3. Acheson K, Schutz Y, Bessard T, Ravussin E, Jéquier E, Flatt JP. Nutritional influences on lipogenesis and thermogenesis after a carbohydrate meal. Am J Physiol 1984;246:E62–70.
4. Wolfe R, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by glucose and fatty acids. N Engl J Med 1987;317:403–8.
5. Shulman GI, Ladenson PW, Wolfe MH, Ridgway EC, Wolfe RR. Substrate cycling between gluconeogenesis and glycolysis in euthyroid, hypothyroid, and hyperthyroid man. J Clin Invest 1985; 76:757–64.

6. Golay A, Schutz Y, Meyer HU, et al. Glucose-induced thermogenesis in nondiabetic and diabetic obese subjects. Diabetes 1982; 31:1023–8.
7. Schutz Y, Thiébaud D, Acheson KJ, Felber JP, DeFronzo RA, Jéquier E. Thermogenesis induced by five different intravenous glucose/insulin infusions in healthy young men. Clin Nutr 1983;2:93–6.
8. Thiébaud D, Schutz Y, Acheson K, et al. Energy cost of glucose storage in human subjects during glucose-insulin infusions. Am J Physiol 1983;244:E216–21.
9. Acheson K, Jéquier E, Wahren J. Influence of β-adrenergic blockade on glucose-induced thermogenesis in man. J Clin Invest 1983; 72:981–6.
10. Welle S, Lilavivathana U, Campbell RG. Increased plasma norepinephrine concentrations and metabolic rates following glucose ingestion in man. Metabolism 1980;29:806–9.
11. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta L, Landsberg L. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 1981;30:219–25.
12. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. J Clin Invest 1991;87:2246–52.
13. Kusaka M, Ui M. Activation of the Cori cycle by epinephrine. Am J Physiol 1977;232:E145–55.
14. Nacht CA, Christin L, Temler E, Chioléro R, Jéquier E, Acheson KJ. Thermic effect of food: possible implication of parasympathetic nervous system. Am J Physiol 1987;253:E481–8.
15. Dériaz O, Nacht CA, Chioléro R, Jéquier E, Acheson KJ. The parasympathetic nervous system and the thermic effect of glucose/insulin infusions in humans. Metabolism 1989;38:1082–8.
16. Schneeberger D, Tappy L, Temler E, Jeanprêtre N, Jéquier E. Effects of muscarinic blockade on the thermic effect of oral or intravenous carbohydrate. Eur J Appl Physiol 1991;63:242–9.
17. Shaw SN, Elwyn DH, Askanazi J, Iles M, Schwarz Y, Kinney JM. Effects of increasing nitrogen intake on nitrogen balance and energy expenditure in nutritionally depleted adult patients receiving parenteral nutrition. Am J Clin Nutr 1983;37:930–40.
18. Tappy L, Acheson K, Normand S, et al. Effects of iv glucose-amino acid on glucose metabolism in lean humans. Diabetes 1991;40(suppl 1):417 (abstr 105A).
19. Thiébaud D, Acheson K, Schutz Y, et al. Stimulation of thermogenesis in men after combined glucose long-chain triglyceride infusion. Am J Clin Nutr 1983;37:603–11.
20. Chen M, Whistler RL. Metabolism of D-fructose. Adv Carb Chem Biochem 1977;34:285–343.
21. Gitzelmann R, Steinmann B, Van den Berghe G. Disorders of fructose metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. 6th ed. New York: McGraw-Hill Information Services Company, 1989:399–424.
22. Marks V, Flatt P. The metabolism of sugars and starches. In: Dobbing J, ed. Dietary starches and sugars in man: a comparison. London: Springer-Verlag, 1989:135–50.
23. Heinz F, Lamprecht W, Kirsch J. Enzymes of fructose metabolism in human liver. J Clin Invest 1968;47:1826–32.
24. De Kalbermatten N, Ravussin E, Maeder E, Geser C, Jéquier E, Felber JP. Comparison of glucose, fructose, sorbitol and xylitol utilization in humans during insulin suppression. Metabolism 1980; 29:62–7.
25. Tappy L, Randin JP, Felber JP, et al. Comparison of thermogenic effect of fructose and glucose in normal humans. Am J Physiol 1986;250:E718–24.
26. Björkman O, Felig P. Role of the kidney in the metabolism of fructose in 60-hour fasted humans. Diabetes 1982;31:516–20.
27. Nilsson L, Hultman E. Liver and muscle glycogen in man after glucose and fructose infusion. Scand J Clin Lab Invest 1974;33:5–10.
28. Katz J, Golden S, Wals PA. Glycogen synthesis by rat hepatocytes. Biochem J 1979;180:389–402.
29. Macdonald I. Differences in dietary-induced thermogenesis following the ingestion of various carbohydrates. Ann Nutr Metab 1984;28:226–30.
30. Schwarz JM, Schutz Y, Froidevaux F, et al. Thermogenesis in men and women induced by fructose vs glucose added to a meal. Am J Clin Nutr 1989;49:667–74.
31. Bergström J, Hultman E. Synthesis of muscle glycogen in man after glucose and fructose infusion. Acta Med Scand 1967;182:93–107.
32. Schwarz JM, Tappy L. Effect of fructose infusion on glucose production. Diabetes 1991;40(Suppl 1):1019 (abstr 255A).
33. Acheson KJ, Schwarz JM. Sympathetic component of fructose thermogenesis. Diabetes 1991;40(Suppl 1):1014 (abstr 254A).
34. Tappy L, Felber JP, Jéquier E. Energy and substrate metabolism in obesity and postobese state. Diabetes Care 1991;14:1180–8.
35. Ravussin E, Acheson KJ, Vernet O, Danforth E, Jéquier E. Evidence that insulin resistance is responsible for the decreased thermic effect of glucose in human obesity. J Clin Invest 1985;76:1268–73.
36. Simonson DC, Tappy L, Jéquier E, Felber JP. Normalization of carbohydrate-induced thermogenesis by fructose in insulin-resistant states. Am J Physiol 1988;254:E201–7.
37. Liu G, Coulston AM, Hollenbeck CB, Reaven GM. The effects of sucrose content in high and low carbohydrate diets on plasma glucose, insulin, and lipid responses in hypertriglyceridemic humans. J Clin Endocrinol Metab 1984;59:636–41.
38. Reiser S, Hallfrisch J. Metabolic effects of dietary fructose. Boca Raton, FL: CRC Press, 1989.
39. Hollenbeck CB. Dietary fructose effects on lipoprotein metabolism and risk for coronary artery disease. Am J Clin Nutr 1993; 58(suppl):800S–9S.
40. Gerrits PM, Tsalikian E. Diabetes and fructose metabolism. Am J Clin Nutr 1993;58:796S–9S.
41. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. Am J Clin Nutr 1980;33:273–8.
42. Zavaroni I, Sander S, Scott S, Reaven GM. Effect of fructose feeding on insulin secretion and insulin action in the rat. Metabolism 1980;29:970–3.
43. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension 1987; 10:512–6.
44. Reaven GM, Ho H, Hoffmann BB. Somatostatin inhibition of fructose-induced hypertension. Hypertension 1989;14:117–20.
45. Crapo PA, Kolterman OG, Henry RR. Metabolic consequence of two-week fructose feeding in diabetic subjects. Diabetes Care 1986;9:111–9.
46. Bantle JP. Clinical aspects of sucrose and fructose metabolism. Diabetes Care 1989;12:56–61.
47. Macdonald I. The effects on energy input and output of dietary starches and sugars. In: Dobbing J, ed. Dietary starches and sugars in man: a comparison. London: Springer-Verlag, 1989:181–91.
48. Macdonald I, Taylor J. Differences in body weight loss on diets containing either sucrose or glucose syrup. Guy's Hosp Rep 1973;122:155–9.
49. Macdonald I. A non-linear relationship between energy intake and rate of weight loss in rats. J Physiol (Lond) 1985;362:40P.