

Research Report

# Low-carbohydrate diets cause obesity, low-carbohydrate diets reverse obesity: A metabolic mechanism resolving the paradox

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## Abstract

High-fat diets produce obesity in part because, per calorie, glucose produces greater post-prandial thermogenesis than lipids, an effect probably mediated by glucose-sensing neurons. A very low-carbohydrate/high-fat/high-protein Atkins-type diet produces obesity but is marginally ketogenic in mice. In contrast, high-sucrose/low-fat diets, and very low-carbohydrate/high-fat/low-protein (anti-epileptic) ketogenic diets reverse diet-induced obesity independent of caloric intake. We propose that a non-ketogenic high-fat diet reduces glucose metabolism and signaling in glucose-sensing neurons, thereby reducing post-prandial thermogenesis, and that a ketogenic high-fat diet does not reduce glucose signaling, thereby preventing and/or reversing obesity.

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## Do low-carbohydrate diets promote or reverse obesity?

“A systematic review of low-carbohydrate diets found that the weight loss achieved is associated with the duration of the diet and restriction of energy intake, but not with restriction of carbohydrates.” (Astrup, Meinert Larsen, & Harper, 2004)

“This review covers evidence from carefully controlled laboratory studies, clinical trials, studies in populations at high risk of developing obesity, and epidemiologic studies on the role of sugars, particularly sucrose, in the development of obesity. Although many environmental factors promote a positive energy balance, it is clear that the consumption of a low-carbohydrate, high-fat diet increases the likelihood of weight gain.” (Saris, 2003)

These two statements, from recent reviews, neatly state the current consensus regarding the effect of dietary composition on obesity. In fact, despite the enormous popularity of low-carbohydrate diets such as the Atkins diet, the South Beach diet, and the Zone diet, the

professional consensus is that low-carbohydrate diets (which typically implies high-fat diets) are more likely to produce obesity than reverse obesity. Although several studies have reported that low-carbohydrate diets are slightly better than low-fat diets to reduce body weight over a period of about 4–6 months (Brehm, Seeley, Daniels, & D'Alessio, 2003; Brehm et al., 2004; Foster et al., 2003), the differences were not significant after a year (Foster et al., 2003; Stern et al., 2004). Similarly, recent “low-glycemic” diets have been promoted as useful for weight loss (Ludwig, 2003). It must be emphasized, however, that other studies have failed to support that low-carbohydrate diets (Astrup et al., 2004; Lean & Lara, 2004; Meckling, O'Sullivan, & Saari, 2004; Truby et al., 2004) or low-glycemic diets (Sloth et al., 2004) are effective for long-term maintenance of weight loss. Similarly, although under certain circumstances access to sucrose, separately from protein, can lead to over-consumption and increased adiposity, this phenomenon appears to occur due to a requirement to obtain sufficient protein and the effect is not observed when protein concentrations are sufficiently high (Kanarek, Aprille, Hirsch, Gualtiere, & Brown, 1987). Certainly, many studies have demonstrated the beneficial

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effects of high-carbohydrate, low-fat diets (e.g., the Mediterranean diet (Schroder, Marrugat, Vila, Covas, & Elosua, 2004)) to reduce adiposity and other aspects of the metabolic syndrome.

### How do low carbohydrate diets promote obesity?

Considerable evidence supports that high-fat diets produce obesity in part because they produce a more metabolically efficient state (Surwit et al., 1995). Although for some diets and genotypes, fats may also be more palatable and therefore, increased caloric consumption may also contribute to diet-induced obesity, high fat diets can produce obesity even when consumed isocalorically with low-fat diets (Surwit et al., 1995). For example, matching caloric intake in rats on a high-fat vs. a low-fat diet causes increased adiposity in the calorie-matched high-fat group (Woods, Seeley, Rushing, D'Alessio, & Tso, 2003). It should be noted that the key observation that diets of different compositions differ in their effect on metabolic efficiency is not inconsistent with the laws of thermodynamics (Feinman & Fine, 2004).

The reason that high-fat diets produce a more metabolically efficient state may be that glucose produces more post-prandial thermogenesis than fats (Westerterp, 2004). Specifically, increasing plasma glucose either by infusion (King, McMahon, & Almond, 1986) or ingestion (Rothwell, Stock, & Warwick, 1983) increases metabolic rate. However, per calorie, carbohydrates produce about three-fold more thermogenesis than fat (Almind & Kahn, 2004; Westerterp, 2004). At least part of glucose-induced thermogenesis is mediated by neuroendocrine mechanisms, since infusion of glucose directly into either the third ventricle or into the periphery produces similar enhancement of metabolic rate (Le Feuvre, Woods, Stock, & Rothwell, 1991), probably via activation of the sympathetic nervous system whose sensitivity to glucose may play a role in the development of obesity (de Jonge & Bray, 2002; Landsberg & Krieger, 1989). Furthermore, 2-deoxyglucose (2-DG) reduces temperature through effects on hypothalamic neurons, apparently via the autonomic nervous system (Shiraishi & Mager, 1980a,b). Similarly, infusion of 2-DG into the ventromedial hypothalamus activates peripheral autonomic responses (Borg, Sherwin, During, Borg, & Shulman, 1995), and infusions of glucose into the hypothalamus block autonomic responses to peripheral hypoglycemia (Borg, Sherwin, Borg, Tamborlane, & Shulman, 1997).

Although acute effects of glucose on metabolic rate are well-documented, to our knowledge only three studies, one published (He, White, Edwards, & Martin, 1998) and two unpublished from our laboratory, have addressed if reduced glucose signaling leads to long-term increases in adiposity. The published study (He et al., 1998) examined the effect of infusing 5-thiogluconate (5-TG) into the fourth ventricle of rats for 14 days. When acutely infused into the fourth ventricle or brainstem, 5-TG produces local

glucopenia leading to acute hyperphagia and other neuroendocrine responses similar those produced by 2-DG or hypoglycemia (Ritter, Dinh, & Zhang, 2000; Ritter, Slusser, & Stone, 1981). When infused for 14 days, the effects to increase food intake are rapidly lost, similar to the effects of repetitive exposure to 2-DG (Sanders & Ritter, 2000). Nevertheless, chronic infusion of 5-TG caused increased weight of the retroperitoneal and parametrial fat pad depots and increased adiposity as determined by body composition measurements. Similarly, we have demonstrated that chronic 2-DG produces strikingly increased adiposity in the nematode *C. elegans* without increasing food intake (Yen & Mobbs, 2004). Finally, we have demonstrated that mice lacking one allele of the glucokinase gene, a key component of the hypothalamic glucose-sensing mechanism (Dunn-Meynell, Routh, Kang, Gaspers, & Levin, 2002; Yang, Kow, Funabashi, & Mobbs, 1999; Yang, Kow, Pfaff, & Mobbs, 2004), become more obese, and exhibit higher plasma leptin and insulin, on a high-fat diet than wild-type controls, without consuming more calories than controls (Yang, Mastaitis, & Mobbs, 2004). Taken together, these studies support that glucose signaling in the brain plays a key role in long-term regulation of energy balance, mainly through a metabolic rather than behavioral mechanism.

### How do low carbohydrate diets reverse obesity?

Therefore, these studies predict that low-carbohydrate, high-fat diets should produce obesity, rather than reverse obesity. These considerations suggest that low-carbohydrate diets may facilitate weight loss in humans (when they do) through psychological, social, or economic mechanisms that overcome the biochemical mechanisms mediating high-fat-induced obesity. However, as described below, ketogenic diets may activate other mechanisms. To address this hypothesis, we assessed if an Atkins-type low-carbohydrate (5% by calories), standard protein (20% by calories), high-fat (76%) diet would promote weight loss in mice made obese by a standard high-fat (45%), moderate carbohydrate (35%) standard protein (20%) diet (Isoda, Schwartz, Mohan, & Mobbs, 2004). For comparison, another group of obese mice was placed on a high simple carbohydrate (corn syrup, 75%) low fat (5%) diet. After switching to the new diets, mice on the Atkins-type low-carbohydrate diet continued to gain weight, whereas the corn syrup diet produced a rapid restoration of body weight (as well as all other aspects of metabolic control such as insulin sensitivity) similar to that observed in chow fed mice. Interestingly, mice on the corn syrup diet ate the same number of calories as mice on the Atkins-type diet (e.g., mice on the corn syrup diet actually ate more mass) but the mice on the corn syrup diet nevertheless rapidly lost weight whereas mice on the Atkins-type diet gained weight. These observations suggest that a high simple carbohydrate diet entails a higher average metabolic rate than a high-fat diet, as had been previously suggested (Surwit et al., 1995).

On the other hand, we observed that the very low-carbohydrate diet (even when carbohydrate was reduced almost to zero) did not significantly increase blood ketone concentration, and produced only a modest effect to reduce blood glucose. We hypothesized that the plasma glucose was derived largely from gluconeogenesis due to the relatively high concentration of amino acids in the diet. It should be noted that the true ketogenic diet used clinically to control epilepsy entails a much lower concentration of protein (8% by calories) than is recommended for Atkins-type diets (20%). When we reduced the protein concentration to 8% (still maintaining carbohydrate at only 5%), adiposity was reversed as rapidly as occurred on the high-sucrose diet. Interestingly, mice on the ketogenic diet consumed the same number of calories as mice on the Atkins-type diet, but rapidly lost weight anyway. This comparison again suggests that metabolic efficiency plays a key role in diet-induced obesity and its reversal by ketogenic diets.

These studies clearly suggest that ketogenic diets produce a less metabolically efficient state than high-fat non-ketogenic diets, so if conditions can be produced which enhance conversion of lipids to ketones, metabolic rate per calorie is effectively increased, consistent with previous reports that chronic infusion of ketones into the brain reduce body weight (Davis, Wirtshafter, Asin, & Brief, 1981). It should be noted, however, that the ketogenic diet is no more effective than the high-sugar diet in reversing diet-induced obesity. Nevertheless, it was surprising that a ketogenic diet would be so effective in reversing obesity in the presence of such high concentrations of (metabolically efficient) fats.

We propose that ketones reverse obesity by counteracting the effect of a high-fat diet to impair glucose metabolism (Atkins, 1998). We (Yang et al., 1999, 2004) and others (Dunn-Meynell et al., 2002; Lee, Li, Xi, Suh, & Martin, 2005) have previously demonstrated that hypothalamic glucose-sensing neurons sense glucose through its metabolism, similar to the glucose-sensing mechanism of pancreatic beta cells (Newgard & McGarry, 1995). However, we (Yang et al., 1999, 2004), and others (Ainscow, Mirshamsi, Tang, Ashford, & Rutter, 2002; Fioramonti, Lorsignol, Taupignon, & Penicaud, 2004) have argued that ATP is not the key metabolic signal in neuroendocrine hypothalamic responses to glucose. Instead, we have argued that the key metabolic signal is NADH (Yang et al., 1999, 2004). Consistent with basic principles of biochemistry (e.g., the lac operon), we also have evidence from microarray studies that glucose induces glycolytic capacity and inhibits beta oxidation whereas a high-fat diet reduces glycolytic capacity and stimulates beta oxidation. Since cytoplasmic NADH is a unique signature of glycolysis (as opposed to ATP, which reflects both glycolysis and beta oxidation), we hypothesize that glucose-induced gene expression is mediated through changes in NADH, not ATP. Lipids would be less efficient at producing NADH, since beta oxidation produces

FADH<sub>2</sub> instead of NADH. However, in contrast to beta oxidation of lipids, the mitochondrial metabolism of ketone bodies produces NADH, not FADH<sub>2</sub>. We, therefore, propose that high-fat non-ketogenic diets lead to obesity because free fatty acids reduce glycolysis in glucose-sensing hypothalamic neurons. We further propose that ketogenic diets reverse obesity by preventing the inhibitory effect of lipids on glycolysis, thus maintaining relatively elevated post-prandial thermogenesis.

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