TOPICAL REVIEW

Insulin resistance and elevated triglyceride in muscle: more important for survival than 'thrifty' genes?

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Elevated intramyocellular triglyceride (IMTG) is strongly associated with insulin resistance, though a cause and effect relationship has not been fully described. Insulin sensitivity and IMTG content are both dynamic and can alter rapidly in response to dietary variation, physical activity and thermoregulatory response. Physically active humans (athletes) display elevated IMTG content, but in contrast to obese persons, are insulin sensitive. This paradox has created confusion surrounding the role of IMTG in the development of insulin resistance. In this review we consider the modern athlete as the physiological archetype of the Late Palaeolithic hunter–gatherer to whom the selection pressures of food availability, predation and fluctuating environmental conditions applied and to whom the genotype of modern man is virtually identical. As food procurement by the hunter–gatherer required physical activity, 'thrifty' genes that encouraged immediate energy storage upon refeeding after food deprivation (Neel, 1962) must have been of secondary importance in survival to genes that preserved physical capacity during food deprivation. Similarly genes that enabled survival during cold exposure whilst starved would be of primary importance. In this context, we discuss the advantage afforded by an elevated IMTG content, and how under these conditions, a concomitant muscle resistance to insulin-mediated glucose uptake would also be advantageous. In sedentary modern man, adiposity is high and skeletal muscle appears to respond as if a state of starvation exists. In this situation, elevated plasma lipids serve to accrue lipid and induce insulin resistance in skeletal muscle. Reversal of this physiological state is primarily dependant on adequate contractile activity, however, in modern Western society, physical inactivity combined with abundant food and warmth has rendered IMTG a redundant muscle substrate.

Introduction

An association exists between body adiposity and impaired carbohydrate metabolism (Coon *et al.* 1989). This association is such that overweight persons who become fatter develop an impaired ability to clear glucose from the blood (Rosenbaum *et al.* 2000) and obese persons losing body fat increase glucose tolerance (Coon *et al.* 1989; Colman *et al.* 1995). The prime cause of this impaired glycaemic control is a resistance in some tissues to the effects of insulin on glucose uptake. This insulin resistance when untreated often leads to type 2 diabetes, a 'disease' condition afflicting approximately 6% of the Western population (Black, 2002). Indeed obesity and the associated insulin resistance have been recently referred to as an 'epidemic' in both the United States and Australia (Zimmet *et al.* 2001).

The continuum between adiposity and impaired carbohydrate metabolism has led to the belief that the extra energy stored by the body as fat is causative in the development of insulin resistance. Consequently, much work has and is being done in an attempt to elucidate the mechanisms that underlie this association.

This review will focus on recent research highlighting the association between plasma free fatty acid concentration, intramuscular triglyceride (IMTG) content and insulin resistance. Using a teleological perspective, we discuss how both muscle insulin

resistance and a concurrent elevation of IMTG would afford a survival advantage during periods of starvation by ensuring adequate fuel for necessary muscle function whilst protecting remaining blood glucose for the brain. Booth *et al.* (2000) have proposed that our (selected) genotype requires the stimulus of physical activity for optimal health, and it is in this context that strategies for the prevention and treatment of insulin resistance are briefly discussed.

'Thrifty' genes

The association between adiposity and insulin resistance and its high incidence in the developed world suggests that rather than being a 'disease' insulin resistance is a normal phenotypic response to protracted caloric surplus caused by excessive energy intake and/or physical inactivity. If so, it also implies that this genotype has, at some period in human evolution, been beneficial to survival and therefore selected for. From such reasoning sprung the 'thrifty' genotype hypothesis (Neel, 1962). This theory proposes that genes allowing conservation of glucose and efficient storage of energy as fat during periods of food abundance aid survival during subsequent food scarcity (Fig. 1). However, these previously beneficial genes become deleterious in affluent populations because the advent of agriculture and trade has removed prolonged caloric deficit as a selection pressure. Although detrimental in affluence, the 'thrifty' genes have survived the advent of agriculture and food preservation techniques because the deleterious phenotype is exposed well after sexual maturation.
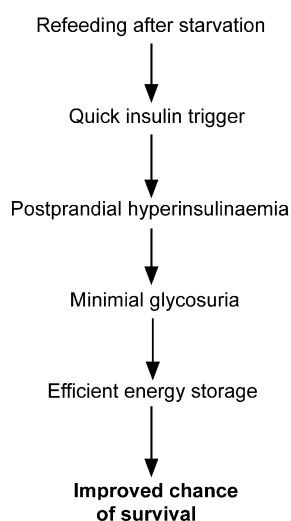
Factors affecting whole-body insulin sensitivity in healthy individuals

Sensitivity to insulin is a physiological process that, in healthy individuals, is rapidly altered in response to changing environmental pressures such as temperature fluctuations and food availability.
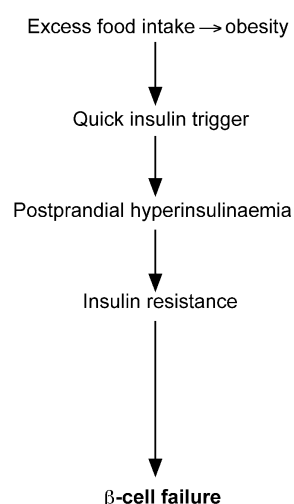
Whole-body insulin sensitivity is acutely improved following a single bout of exercise (Perseghin *et al.* 1996), but the effect is transient and appears to be proportional to exercise severity (Thompson *et al.* 2001). Chronic physical activity is also associated with improved insulin sensitivity (King *et al.* 1987; Rodnick *et al.* 1987) yet this adaptation is also rapidly diminished within six days of cessation of regular exercise (Mikines *et al.* 1989; Vukovich *et al.* 1996). Although resumption of training after short-term (10 days) inactivity restores glucose tolerance to near preinactivity levels (Heath *et al.* 1983), insulin sensitivity is not fully recovered (Dela *et al.* 1992), indicating a less plastic adaptive effect of training distinct from that of acute exercise.

In animals, whole-body and muscle insulin-mediated (Vallerand *et al.* 1990) and non-insulin-mediated (Shibata *et al.* 1989) glucose disposal improves with acute (48 h) exposure to cold. Although there has been little recent

A. Hunter-gatherer with "thrifty" genes

Refeeding after starvation

↓

Quick insulin trigger

↓

Postprandial hyperinsulinaemia

↓

Minimial glycosuria

↓

Efficient energy storage

↓

Improved chance of survival

B. Modern individual with "thrifty" genes

Excess food intake → obesity

↓

Quick insulin trigger

↓

Postprandial hyperinsulinaemia

↓

Insulin resistance

↓

β-cell failure

Figure 1.
The survival advantage of a 'quick insulin trigger' as suggested by Neel (1962) and how this was proposed to aid survival in primitive man (*A*) but produce diabetes in modern man (*B*). (Diagram adapted from Reaven, 1998).

research in this area, and no equivalent studies have been performed on humans, these observations in animals may, akin to the effects of exercise, be a result of shivering-induced skeletal muscle contractile activity.

Dietary interventions are also known to induce rapid changes in insulin sensitivity. Insulin sensitivity is decreased in response to a short-term (3 day) high fat diet (Bachmann *et al.* 2001) or calorie restriction (Webber *et al.* 1994; Gazdag *et al.* 2000). The latter effect is evident as little as 14 h after the last meal (Horowitz *et al.* 2001).

Insulin sensitivity can also be rapidly altered in response to artificial manipulation of plasma free fatty acid (FFA) levels. An increase in FFAs via lipid/heparin infusion reduces insulin sensitivity within 4 h (Roden *et al.* 1996; Boden *et al.* 2001), whilst overnight administration of Acipimox lowers FFAs and improves insulin sensitivity in both lean and obese subjects (Santomauro *et al.* 1999).

A raised plasma FFA concentration has for sometime been implicated in dietary-induced insulin resistance. This was thought to occur in the liver and muscle via the glucose fatty-acid cycle. Glycolysis, and thence glucose uptake, is inhibited by increases in acetyl-CoA and NADH derived from lipid and ketone substrates (Randle *et al.* 1963). More recently, however, it has been shown that when FFA levels are acutely elevated following lipid/heparin infusion, skeletal muscle glucose-6-phosphate levels fall below control levels, indicating inhibition of glucose transport/phosphorylation (Roden *et al.* 1996; Krebs *et al.* 2001). Thus, raised plasma FFA availability may induce insulin resistance via inhibition of glucose transport, rather than inhibition of glycolysis via operation of the glucose fatty-acid cycle.

Triglyceride and insulin resistance in muscle

Skeletal muscle is the primary site of insulin action and is thus inherently linked to the development of whole-body insulin resistance. The mechanism by which raised plasma FFA concentrations may inhibit insulin-stimulated glucose uptake in muscle is not yet fully understood and is likely to be polygenic (Kraegen & Cooney, 1999). However, recent improvements in the ability to measure IMTG content *in vivo* have implicated these fatty acids stored within the muscle fibre as a 'middle man' in the insulin resistance–FFA relationship. In both normal and obese subjects, IMTG content is inversely associated with whole-body insulin sensitivity (Forouhi *et al.* 1999; Jacob *et al.* 1999; Krssak *et al.* 1999; Perseghin *et al.* 1999; Virkamaki *et al.* 2001; Goodpaster *et al.* 2001; Greco *et al.* 2002), inferring a causal relationship independent of whole-body

adiposity. Support for this is found via the observation that, in healthy subjects, inducing an increase in IMTG content via 4–5 h lipid/heparin infusion reduces whole-body sensitivity to insulin (Boden *et al.* 2001; Brechtel *et al.* 2001).

The mechanism behind the close coupling of IMTG content and inhibition of insulin-stimulated glucose uptake in muscle is yet to be elucidated, although it appears unlikely that IMTG itself directly impairs insulin action. Rather, an increase in some related fatty acid moiety such as long chain acyl-CoA, ceramide or diacylglycerol, whose appearance is related to elevations in IMTG content, may disturb normal insulin-signalling pathways (Schmitz-Peiffer *et al.* 1999; Ellis *et al.* 2000; Itani *et al.* 2002). The mechanisms via which these may occur have been recently reviewed in detail elsewhere (Kelley *et al.* 2002; McGarry, 2002; Hegarty *et al.* 2003). However, that some homogenous groups characterisd by ethnicity (Forouhi *et al.* 1999; Misra *et al.* 2003) or high physical activity levels (Goodpaster *et al.* 2001; Thamer *et al.* 2003) fail to exhibit an inverse correlation between IMTG content and insulin sensitivity suggests that the conjunction is not simply linear and that other factors may influence the relationship. The precise mechanism notwithstanding, the weight of evidence suggests an elevated IMTG content almost certainly contributes to the development of muscle insulin resistance (McGarry, 2002) and type 2 diabetes (Kelley *et al.* 2002).

Physiology of IMTG

Cross-sectional studies of children (Ashley *et al.* 2002), adolescents (Sinh *et al.* 2002) and adults (Greco *et al.* 2002) show a direct correlation between whole-body adiposity and IMTG content. Furthermore, reductions in body fat are associated with a reduced IMTG content (Greco *et al.* 2002). Thus, there is a strong link between body fat content and muscle triglyceride.

Elevations in IMTG can be induced within hours with lipid/heparin infusion (Bachmann *et al.* 2001; Boden *et al.* 2001), while formation (in animals) can be curbed if lipolysis (and thus FFA concentration) is inhibited by nicotinic acid administration (Stankiewicz-Choroszucha & Gorski, 1978). Similarly, in healthy individuals, a high carbohydrate diet is a potent inhibitor of IMTG formation (Kiens, 1998; Coyle *et al.* 2001; Decombaz *et al.* 2001; Larson-Meyer *et al.* 2002), also probably via suppressing FFA availability. In contrast IMTG content is increased with a high fat diet (Bachmann *et al.* 2001; Decombaz *et al.* 2001) or fasting (Krssak *et al.* 2000; Stannard *et al.*

2002), conditions associated with elevated circulating lipid concentrations.

IMTG can be oxidized during exercise, though this is limited to the active musculature (Sacchetti *et al.* 2002). Although there is some evidence to the contrary (Jansson & Kaijser, 1982; Kayar *et al.* 1986; Kiens *et al.* 1993; Wendling *et al.* 1996), the majority of studies indicate that this endogenous lipid store is measurably reduced during prolonged contractile activity (Johnson *et al.* 2002; Watt *et al.* 2002*a,b*), and this is accentuated when dietary carbohydrate intake is restricted (Stankiewicz-Choroszucha & Gorski, 1978; Johnson *et al.* 2002).

Measurement of IMTG utilization or accretion using pre- and postintervention measurement (^{1}H-MRS or biochemical and histological methods) are insensitive to the labile nature of the IMTG pool and are unable to measure IMTG turnover. Studies combining ^{14}C-prelabelled IMTG and ^{13}C-labelled FFAs reveal simultaneous hydrolysis and reesterification within muscle (Guo *et al.* 2000), favouring net hydrolysis during exercise (Dyck *et al.* 2001) and reesterification at rest provided FFA availability is adequate (Dyck *et al.* 2000). If these processes occur simultaneously at an equivalent rate, no absolute change in IMTG content would be observed (Dyck & Bonen, 1998; Guo *et al.* 2000), though fatty acids originally contained within IMTG stores may have been utilized.

Observations of net IMTG degradation, yet simultaneous glycogen repletion, in humans fed high carbohydrate in the postexercise period imply that a further role of IMTG may be to support muscle metabolism during recovery from exhaustive exercise, thereby enabling optimal carbohydrate preservation (Kiens, 1998). However, this finding is not replicated when no food (Krssak *et al.* 2000), high fat (Decombaz *et al.* 2000, 2001) or mixed (Decombaz *et al.* 2000) diets are given in recovery. Therefore, attenuation of IMTG repletion observed with a high carbohydrate recovery diet (Kiens, 1998; Coyle *et al.* 2001; Decombaz *et al.* 2001; Larson-Meyer *et al.* 2002) may result from suppressed FFA availability (Kiens, 1998), and if a stimulus for IMTG hydrolysis such as adrenaline (Watt *et al.* 2003) persists in the immediate postexercise period, IMTG levels could decrease.

In rodents, shivering-induced muscle contractile activity results in IMTG utilization during cold exposure (Gorski *et al.* 1981). Whilst no similar direct data is available in cold-exposed humans, indirect measurements suggest net muscle IMTG metabolism (Martineau & Jacobs, 1989), which like exercise, is accentuated when endogenous carbohydrate stores are low (Martineau & Jacobs, 1991).

Thus, the IMTG 'pool' is highly dynamic and represents a balance between the processes of formation (which is primarily a function of circulating fatty acid availability), and degradation (which is largely a function of contractile activity). The net effect of these opposing processes may range from a slow and subtle to a large and rapid change in IMTG content, during which time turnover may be fast or slow. Elevated IMTG in obesity may thus reflect a chronically elevated blood lipid profile, an alteration in triglyceride–fatty acid cycling within the muscle, and/or a chronically low muscle lipid oxidation in these individuals.

It can be seen from the above discussion that situations in which IMTG is elevated, such as a high fat diet, fasting and artificial plasma FFA elevation, are also associated with insulin resistance. Conversely, muscular activity (via exercise or shivering), the only known non-pharmacological intervention that directly reduces IMTG, is associated with enhanced insulin sensitivity. However, the apparent relationship between elevated IMTG and insulin resistance becomes uncoupled when physical fitness is considered (Thamer *et al.* 2003). Physically active individuals (athletes), who have high insulin sensitivity (Goodpaster *et al.* 2001), paradoxically exhibit elevated IMTG concentrations (Hoppeler *et al.* 1973; Goodpaster *et al.* 2001), whereas the insulin resistant obese also display elevated IMTG (Goodpaster *et al.* 2001; Greco *et al.* 2002). This comparison has contributed to the confusion in the understanding of the physiology of IMTG and its role in insulin resistance.

It is well known that endurance training increases the ability of muscle to utilize lipid during subsequent exercise (Holloszy, 1967; Mole *et al.* 1971; Coggan *et al.* 1993; Martin *et al.* 1993; Poehlman *et al.* 1994; Helge *et al.* 1996; Phillips *et al.* 1996; Bergman *et al.* 1999), but there is dissonance over whether this extra lipid oxidized is of intra or extra-muscular origin (Saltin & Astrand, 1993; Martin, 1997). Studies employing a one-legged training model (Turcotte *et al.* 1992; Kiens *et al.* 1993) show a greater reliance on FFAs during exercise in the trained state. However, an increased reliance on FFA uptake and utilization is at odds with the blunted lipolytic hormone response (Green *et al.* 1991), and consequent reduction in FFA availability (Martin III *et al.* 1993), evident at the same absolute (two-legged) exercise intensity post-training. This incongruency may reflect the different training models used or the very low density lipoproteins (VLDL) triacylglycerol-derived fatty acid contribution (Kiens *et al.* 1987; Kiens *et al.* 1993; Helge *et al.* 2001), though it is argued that the latter remains small (Havel *et al.* 1967). Cross-sectional and longitudinal studies have

demonstrated that endurance training imparts an increase in the capacity of the muscle to store IMTG (Hoppeler *et al.* 1973; Goodpaster *et al.* 2001; Schrauwen-Hinderling *et al.* 2003; Thamer *et al.* 2003) and hence an increase in its contribution as a substrate during exercise (Lithell *et al.* 1979; Hurley & Seals, 1986; Jansson & Kaijser, 1987; Martin III *et al.* 1993). If this is the case, the elevated IMTG content observed in endurance-trained athletes may signify an adaptation designed to ensure sufficient lipid substrate to support subsequent exercise in the presence of reduced FFA delivery (Martin III, 1997). This is supported by the observation that IMTG degradation is significantly attenuated during the later stages of prolonged exercise when plasma FFA availability has substantially increased (Watt *et al.* 2002*a*).

Physical capacity *versus* efficient energy storage in selection

It is proposed that the last significant period of selection pressure applied in the genetic development of man occurred during the Late Palaeolithic prior to the development of agriculture (Barnes, 1968; Washburn, 1976). The biology of Palaeolithic hunter–gatherer man surmised from fossil records has been used to illustrate the impact that changes in food type and availability (resulting from the development of agriculture and successful food preservation techniques) have had in the development of the modern 'lifestyle' ailments such as type 2 diabetes and cardiovascular disease (Eaton & Konner, 1985; Eaton *et al.* 1999, 2002; Booth *et al.* 2002; Cordain *et al.* 2002). Indeed, the original 'thrifty' genotype hypothesis (Neel, 1962) is based on the assumption that the hunter–gatherer experienced alternating periods of food surfeit and scarcity. Observations of remnant hunter–gatherer communities and the impact of their acculturation to Western lifestyle appear to strengthen the hypothesis that ancient genotypes and modern agriculture combine to result in a deleterious phenotype (Moodie, 1973; O'Dea, 1984).

In hunter–gatherer society, however, physical work and food procurement are inextricably linked (Booth *et al.* 2002; Eaton *et al.* 2002). Physical activity is required to obtain food before the energy in that food can be utilized or stored. The attributes of rapid and efficient storage of energy upon refeeding (the hypothesized role of 'thrifty' genes) are of little survival value if food cannot be first obtained whilst in the fasted state. That is, 'thrifty' genes (Neel, 1962) must have been of secondary importance in survival to genes that preserved physical capacity during food deprivation.

Athletes and hunter–gatherers

In their recent review, Booth *et al.* (2002) compare the physical activity levels of modern Western man with that of the Late Palaeolithic hunter–gatherer. The authors suggest that the de-trained muscles of the relatively sedentary modern man are an important aspect in the development type 2 diabetes. Their argument that habitual exercise in sedentary cultures restores perturbed mechanisms towards the 'normal' physiological range experienced by early man is supported by observations of enhanced insulin sensitivity and the preventative effects of chronic exercise against the development of type 2 diabetes. Booth *et al.* argue that there should be a paradigm shift in what is considered 'normal' physiology away from the sedentary majority towards the physiological characteristics of modern athletes. Such physiological characteristics include a proportionally high muscle and low fat mass and a high oxidative muscle capacity – the opposite to those observed in modern insulin-resistant humans. According to this proposition it is from physically active populations and not obese individuals that an understanding of the role of IMTG in the development of insulin resistance may be made. Thus, the elevated IMTG storage seen in athletes (and presumably hunter–gatherers) may represent part of a *normal* physiological fluctuation in IMTG levels. It is of note that the only situation in which these lean, healthy, normally insulin-sensitive individuals 'naturally' become insulin resistant is with short-term starvation (Mansell & Macdonald, 1990; Webber *et al.* 1994).

From a Darwinian perspective therefore, two questions need to be answered. Firstly, what selection pressures may have existed such that a greater ability to store IMTG was of advantage to survival and procreation, and secondly, what is the further advantage of a concomitant muscle insulin resistance?

The survival advantage of accumulating IMTG

From the results of their studies on fasting conducted in the 1960s (Cahill *et al.* 1966; Owen *et al.* 1967, 1969), Cahill and associates suggested that a crucial aspect of survival during starvation was the ability of the hunter–gatherer to maintain muscle protein (Cahill & Owen, 1968). Maintaining this functional tissue meant that the individual was able to hunt successfully at the first opportunity and also perhaps resist predation (Reaven, 1998). However, an issue not addressed by Cahill *et al.* is the necessity for the 'protected' muscle to contain a readily available substrate to fuel muscle contraction.

For the hunter–gatherer, the majority of energy expenditure in excess of maintenance would have occurred in the physical quest for food and for thermoregulation. To conserve energy, adult humans are inherently lazy, so physical activity would be largely restricted until food was scarce and real hunger was felt. Indeed the amount of energy expended in finding food was probably proportional to the hunger felt, the time since the last meal and, because carbohydrate stores are quickly depleted, inversely proportional to carbohydrate status. As energy deficit increased, physical ability to procure the next meal would have become even more important at the time when endogenous carbohydrate stores would have been challenged.

Cordain *et al.* (2002) argue that the diet of many hunter–gatherers was predominantly of animal origin. Physical activity, sometimes of a strenuous nature, would be required to trap an animal. Therefore, as real hunger is felt and starvation begins, the ability to maintain an endogenous substrate capable of immediately supporting physical activity would prove advantageous to survival.

Muscle glycogen is currently acknowledged as the most important substrate at the onset of exercise and during strenuous contractile activity because: it resides within the muscle fibre; its breakdown is catalysed by contraction; and anaerobic glycogenolysis can rapidly produce ATP. Perhaps for the same reasons, muscle glycogen has also been shown to be a significant substrate in support of shivering-induced thermogenesis (Martineau & Jacobs, 1988; Haman *et al.* 2002). Although fasting alone does not result in muscle glycogen depletion (Knapik *et al.* 1988), depletion during muscle activity followed by limited carbohydrate intake minimizes muscle glycogen accretion (Bergstrom *et al.* 1967; Pernow & Saltin, 1971). Thus, in the postexercised muscle of the hunter–gatherer, muscle glycogen content would remain low after a few days of starvation or a predominantly animal flesh diet. In contrast, plasma FFAs would be in abundant supply. However, FFAs alone could not then fuel the onset of further contractile activity because mobilization from remote depots is under humoral control and at this time lags muscle substrate requirement. In contrast, IMTG, which resides within the muscle fibre, is available for immediate utilization (Romijn *et al.* 1993) and like muscle glycogen its breakdown is activated by contraction (Langfort *et al.* 2000). A period of FFA elevation in a carbohydrate-lowered state provides an ideal environment for IMTG formation.

The survival advantage of elevated IMTG in prehistoric man may have been to provide muscle with an alternative to muscle glycogen as a readily available substrate to support muscle metabolism at the onset of exercise or cold exposure during early starvation or carbohydrate restriction. The recent finding that 72 h of complete food restriction results in a nearly three-fold increase in IMTG in physically trained men (Stannard *et al.* 2002) is salient evidence that under such conditions FFAs from adipose tissue may be re-distributed to skeletal muscle for storage in the form of IMTG. In an evolutionary context, 72 h of food or carbohydrate deprivation is not long and perhaps relatively often experienced. Internment of lipid within the muscle in these situations would allow immediate access of this substrate to fuel the muscle contraction required to obtain the next meal, resist predation and maintain body temperature during cold exposure. In support of this hypothesis are the observations that: (1) when leg muscles are depleted of glycogen by exercise followed by carbohydrate restriction, and FFA availability is simultaneously reduced via nicotinic acid ingestion, the majority of substrate supporting contraction is calculated to have come from IMTG (Pernow & Saltin, 1971); (2) the ability to utilize lipid stores to maintain body temperature via shivering-induced thermogenesis in the glycogen-depleted state is not compromised when FFA availability is simultaneously reduced via nicotinic acid administration (Martineau & Jacobs, 1991).

The survival advantage of reduced muscle glucose uptake

After a short period of starvation, lean individuals show a diminished ability to clear glucose from the bloodstream whether mediated by contraction (Knapik *et al.* 1988) or insulin (Webber *et al.* 1994). This 'fasting diabetes' provides a clear survival advantage in that circulating glucose is spared for use by the brain and other glucose-dependant tissues when liver glycogen stores are depleted. In turn, there is less pressure on the liver and kidney to manufacture glucose from amino acids, essential if functional tissue is to be maintained.

Resistance in muscle to the effects of insulin on glucose uptake may be particularly important during starvation or carbohydrate restriction. The ability of insulin to prevent rampant proteolysis and lipolysis is maintained during short-term starvation, yet its role in stimulating glucose uptake by muscle is prevented (Fryburg *et al.* 1990). This dissociation of insulin actions means the residual circulating insulin levels maintained in short-term starvation (Cahill *et al.* 1966) can attenuate proteolysis,

ketosis and hepatic glucose release, whilst unnecessary utilization of blood glucose by muscle is prevented.

The whole-body effects of impaired muscle glucose disposal and insulin resistance during starvation or carbohydrate restriction would be relatively greater in the athlete/hunter–gatherer than in sedentary modern man because of their greater relative muscle mass and thus greater sink for glucose disposal.

The survival advantage of insulin resistance and elevated IMTG occurring in parallel

The beauty of these two physiological responses occurring in parallel, regardless of the existence of any cause-and-effect relationship, is revealed when muscle contractile activity occurs whilst in the fasted state.

Hepatic glucose release during intense exercise is centrally mediated and proportional to the muscle mass recruited (Vissing, 2000). Resistance to contraction-mediated glucose uptake in fasting allows a sparing of precious blood glucose without the contracting muscle taking advantage of any exercise-induced elevation in blood glucose concentrations (Sonne *et al.* 1987). The concomitant elevated levels of IMTG provide an alternate substrate to muscle glycogen to support contraction

during exercise. Similarly, with cold exposure during fasting, IMTG is available as an adjunct to FFAs to support the involuntary muscle activity of shivering in the absence of significant carbohydrate stores. On cessation of exercise, any increased insulin secretion in response to residual elevated glucose (Marliss *et al.* 2000) would be less effective in promoting muscle glucose uptake. On the other hand, FFA concentrations will be extremely high and provide for rapid synthesis of IMTG, so that if food was not forthcoming, the ability to endure cold nights and hunt/gather could be maintained.

Development of insulin resistance in sedentary modern man

In the light of this discussion, how do these physiological phenomena relate to sedentary, obese modern man and the development of insulin resistance?

Obesity results in a chronically elevated blood lipid profile, largely because of the mass action effect of excessive adipose tissues stores. Therefore in obesity, an 'unnatural' situation for the hunter–gatherer, the elevated blood lipid profile, akin to the circulatory environment experienced in fasting or carbohydrate restriction, acts to trigger the physiological responses for such conditions (Fig. 2). The 'misguided' response is to protect circulating
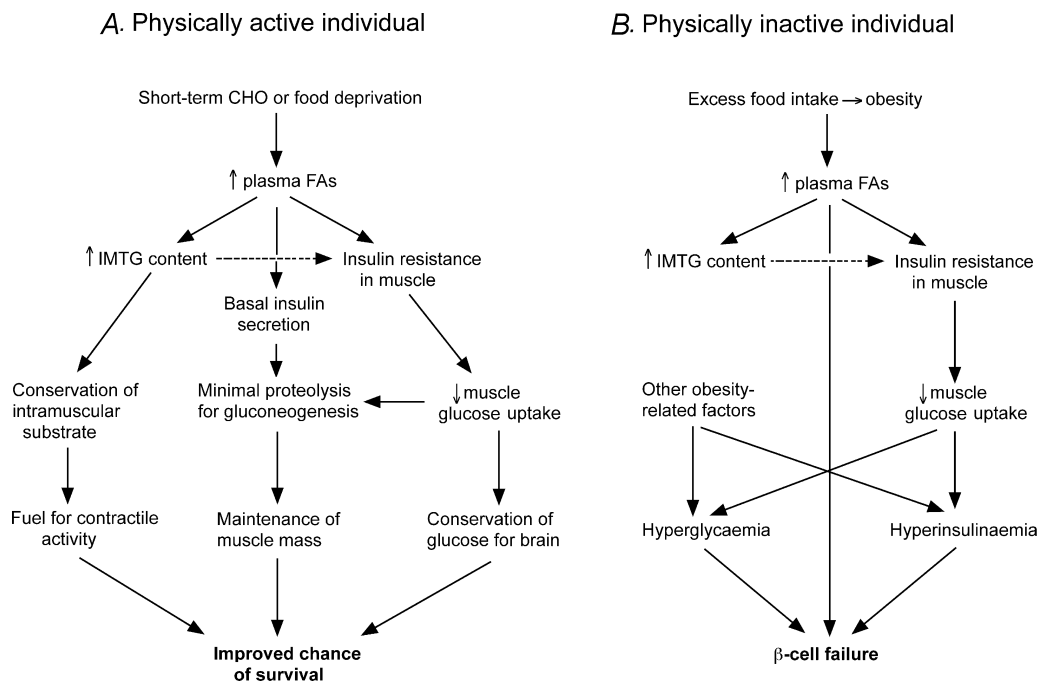
Figure 2.

The survival advantage of muscle insulin resistance and elevated IMTG in physically active individuals during short-term starvation (*A*) and how this same genotype can lead to type 2 diabetes in sedentary individuals when caloric intake is excessive (*B*). Dotted arrow represents a strong association only.

glucose via inhibition of muscle glucose transport whilst accumulating IMTG to ensure a readily available substrate for subsequent contractile activity.

Therefore, irrespective of a causal relationship, concurrent elevation of IMTG and insulin resistance are part of a coordinated physiological response to elevations in circulating fatty acid availability mediated (in our hunter–gatherer ancestors at least) by short-term changes in food availability. Teleologically, these associated and probably related processes were designed to aid survival in an environment where food availability was sporadic. That these processes also occur simultaneously in sedentary Western man indicates an appropriate (or normal) physiological response, but in an inappropriate environment.

Implications in obesity and type 2 diabetes

If elevated IMTG *does* inhibit glucose transport into the muscle, whether directly (Keizer *et al.* 2001) or indirectly via elevated myoplasmic long-chain fatty acyl CoA (Cooney *et al.* 2002), with a chronically elevated blood lipid profile, such as is found in obesity, there will be a protracted period of muscle resistance to insulin-mediated glucose uptake. This in turn may result in hyperinsulinaemia and/or hyperglycaemia which might become chronic unless IMTG levels can be reduced.

This line of reasoning suggests that muscle insulin resistance can be prevented from developing or improved even when adiposity is high by ensuring an adequate rate of lipid oxidation. Indeed, it has been shown that in overweight persons increased rates of postabsorptive lipid oxidation are associated with normal IMTG content and insulin sensitivity (Perseghin *et al.* 2002). Furthermore, persons carrying larger amounts of adipose tissue improve whole-body insulin resistance with participation in an exercise-training programme without changes in body adiposity (Dengel *et al.* 1996), and finally, the inverse relationship between IMTG and insulin sensitivity in Pima Indians is independent of total adiposity (Pan *et al.* 1997). Together these results suggest that obesity alone does not directly cause insulin resistance, but that insulin resistance is prevalent in obesity because obesity elevates blood lipids and IMTG content. Even in obese persons, improving the ability of the muscles to oxidize lipid may prevent IMTG accrual and, in turn, insulin sensitivity can be increased.

A number of studies show a positive correlation between insulin resistance and the proportion of glycolytic muscle fibres in the quadriceps (Hickey *et al.* 1995; Kriketos *et al.* 1996; Lillioja *et al.* 1987). Although muscle fibre type distribution is not a direct measure of oxidative capacity, in the absence of exercise training this inherent characteristic may limit muscle lipid oxidation in some individuals (or homogenous groups), making them more susceptible to muscle insulin resistance.

In the light of our inheritance, how may muscle insulin resistance be reversed to prevent or treat whole-body insulin resistance? One answer may be acute exercise of a sufficient dose to decrease chronically elevated IMTG levels (Thompson *et al.* 2001). However, for an untrained individual whose oxidative capacity is limited, this would prove difficult because other fatigue factors may limit exercise duration prior to significant degradation of IMTG stores. Also, whilst the individual is still obese, an elevated blood lipid profile will remain to encourage reformation of IMTG.

Cold exposure, although shown in animals to potentiate the effects of insulin on muscle glucose uptake (Vallerand *et al.* 1990; Sano & Terashima, 2001) and reverse the diabetogenic effects of a high fat diet (Vallerand *et al.* 1986), would no doubt prove unpopular, and because subcutaneous adipose tissue depots provide insulation, this stimulus would be less effective in obese persons.

Perhaps the only non-pharmacological solution to prevent muscle insulin resistance is to engage in chronic physical activity and improve the capacity of the musculature to utilize fatty acids. In doing so modern man would regain the 'normal' physiology of our hunter–gatherer ancestors in the same way as the modern athlete and express the phenotype as it has evolved to be.

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