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Metabolic flexibility in health and disease

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Summary

Metabolic flexibility is the ability to respond or adapt to conditional changes in metabolic demand. This broad concept has been propagated to explain insulin resistance and mechanisms governing fuel selection between glucose and fatty acids, highlighting the metabolic inflexibility of obesity and type 2 diabetes. In parallel, contemporary exercise physiology research has helped to identify potential mechanisms underlying altered fuel metabolism in obesity and diabetes. Advances in 'omics' technologies have further stimulated additional basic and clinical-translational research to further interrogate mechanisms for improved metabolic flexibility in skeletal muscle and adipose tissue with the goal to prevent and treat metabolic disease.

What is metabolic flexibility?

Metabolic flexibility describes the ability of an organism to respond or adapt according to changes in metabolic or energy demand as well as the prevailing conditions or activity. It was first used as a term describing the increased capacity of helminthes, a parasitic worm, to generate chemical energy and key metabolites either aerobically or by using anaerobic respirations to give it greater versatility and metabolic flexibility to respond and adapt to environmental changes in its habitat (Kohler, 1985).

The more common concept of metabolic flexibility has been promulgated in the context of fuel selection in the transition from fasting to fed states, or fasting to insulin stimulation to explain insulin resistance (Goodpaster and Kelley, 2008). The original Randle Cycle (Randle et al., 1963) was put forth as a tenet to explain elevated fatty acid oxidation and reduced glucose oxidation underlying insulin resistance and type 2 diabetes. Kelley and Mandarino later reconsidered these concepts following a series of elegant *in vivo* limb balance studies demonstrating the *metabolic inflexibility* in human type 2 diabetes and obesity in which, during post-absorptive conditions, skeletal muscle has elevated glucose oxidation and reciprocal reduced fatty acid oxidation (Kelley, 1994, 1993; Kelley and Mandarino, 1990; Kelley et al., 1993). Since those first experiments were described, the term metabolic flexibility has evolved to encompass other metabolic circumstances and tissues and more

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broadly refers to a physiological adaptability. Metabolic flexibility was also inferred to have tissue specificity in response to nocturnal and diurnal fasted and fed conditions (Kelley et al., 1999).

Exercise is another physiological condition requiring metabolic flexibility in order to match fuel availability with the metabolic machinery to meet enormous increases in energy demands. Exercise duration and intensity can each profoundly influence energy demand, thereby taxing energy stores and catabolic pathways in very different ways. Although the topic of exercise-induced changes in metabolism has been covered in recent reviews (see (Egan and Zierath, 2013; Hawley et al., 2014)), the mechanisms underlying metabolic flexibility with exercise deserves further inquiry. “Muscle plasticity” was first used (Pette, 1980) as a term used to characterize muscle’s ability to respond to a variety of stimuli, and included a metabolic flexibility. Exercise training can alter fuel storage and availability, and recent evidence that exercise promotes changes in the skeletal muscle epigenome (Rasmussen et al., 2014), transcriptome (Keller et al., 2011; Raue et al., 2012) and proteome (Hoffman et al., 2015), all of which constitute an anabolic flexibility in order to meet changes in energy requirements for each bout of exercise or activity, merit deeper investigations into the molecular mechanisms driving metabolic flexibility.

Any review or discussion of these general concepts of metabolic flexibility deserves to be placed in some context and framework; for without this, the review could be too broad and unwieldy. We will review the processes and some of the underlying mechanisms of healthy metabolically flexible responses to fasting and feeding and from rest to exercise, and with some inferences to metabolic inflexibility as it relates to pathobiology. Within this context, we will review the evidence that exercise training can improve metabolic flexibility, highly relevant to improving the pathophysiological aspects of obesity, type 2 diabetes and aging. We will also attempt to summarize the evidence comparing and contrasting the effects of exercise training and calorie restriction-induced weight loss on metabolic flexibility, and the implications that this likely has on prevention and treatment of these conditions.

We emphasize the role of skeletal muscle and adipose tissue in metabolic flexibility in humans. These are two tissues, which play a crucial role in energy metabolism, and both can be accessed in humans with biopsies to interrogate their biology and response to acute and chronic interventions. Regardless of tissue, metabolic flexibility is driven by cellular and organelle processes, perhaps most pertinently in the mitochondria. Here we deliberate metabolic flexibility during relevant conditions of fasting, insulin stimulation and exercise. We also discuss some of the cellular aspects of metabolic flexibility that have been re-capitulated *in vitro*.

Fasting to feeding - Insulin resistance as part of the metabolic inflexibility in obesity and type 2 diabetes

Skeletal muscle drives fuel catabolism

The original limb balance indirect calorimetry technique established by Andres and colleagues in 1956 measured glucose and fatty acid oxidation via the Respiratory Quotient

(RQ) of the forearm muscle during post-absorptive conditions (Andres et al., 1956). They clearly demonstrated that that the normal, healthy transition from fasting to feeding involves shifts in fuel selection from predominantly oxidative fatty acid metabolism to more glucose oxidation in skeletal muscle. Kelley and colleagues later demonstrated that this shift also included, albeit to a quantitatively lesser degree, increases in glycolytic energy production (Kelley et al., 1999).

Since energy expenditure, mostly from the thermic effect of food, increases by less than 10% (Acheson et al., 1984), this substrate shift serves to efficiently utilize energy sources based on the content or mixture of the macronutrients in the meal. The primary purpose of this substrate shift is to move from catabolic to anabolic processes in which energy can be effectively stored in skeletal muscle, adipose and liver tissues. Insulin release in response to a meal is a major driver of this shift.

Much of the attention around metabolic flexibility is because of its implication in insulin resistance, a concept first advanced by Wilhelm Falta and published in Vienna in 1931 as a possible underlying cause of type 2 diabetes (Falta and Boller, 1931). During the ensuing 85 years insulin resistance has evolved to become generally accepted as the predominant factor leading to type 2 diabetes, and the most probable single link among a constellation of cardiometabolic risk factors known as the metabolic syndrome linking obesity, type 2 diabetes and cardiovascular disease (Reaven, 1988).

Skeletal muscle insulin resistance and fatty acid metabolism

Insulin resistance is a key component of the metabolic inflexibility that can develop in many tissues and organs. The cellular mechanisms for insulin resistance have been reviewed extensively (Flier et al., 1979; Holland and Summers, 2008; Shulman, 2004). A substantial emphasis on mechanisms underlying insulin resistance in liver and skeletal muscle has been placed on the roles of impaired mitochondrial fatty acid oxidation and excess accumulation of lipid metabolites diacylglycerol and ceramides.

Skeletal muscle accounts for ~60–80% of the increase in glucose metabolism in response to insulin (Ng et al., 2012), and an enormous body of work supports a causal role for skeletal muscle insulin resistance in type 2 diabetes (DeFronzo and Tripathy, 2009; Petersen et al., 2007). Intuitively, a reduction in the amount of glucose entering the muscle cells and adipocytes from the bloodstream, along with a reduced suppression of hepatic glucose production, will elevate glucose in the blood in the absence of a corresponding increase in insulin release from the pancreatic beta cells. Diabetes develops, as the argument goes, if and when the beta cells fail to appropriately compensate for this insulin resistance with higher insulin secretion.

It is difficult to argue against insulin resistance in muscle, adipose tissue and liver causing hyperglycemia with inappropriate or failed beta cell compensation. Insulin resistance often precedes hyperinsulinemia and hyperglycemia (DeFronzo and Tripathy, 2009). There is, however, some debate about whether insulin resistance in muscle is a primary defect or an adaptation in diabetes. Defects in fatty acid oxidation (Kelley et al., 1999; Koves et al.,

2008; McGarry, 1992), altered mitochondrial energetics (Lee et al., 2010; Morino et al., 2005) and intramyocellular lipid accumulation (Amati et al., 2011; Coen et al., 2010) have all been associated with insulin resistance and type 2 diabetes. Contentious debate also continues concerning which tissue or organ is the primary instigator of whole body insulin resistance, glucose intolerance and diabetes. Turner et al. have provided elegant time course evidence in a high-fat-fed rodent model of insulin resistance whereby hepatic insulin resistance precedes both adipose tissue and skeletal muscle insulin resistance (Turner et al., 2013). This study also highlights the important role of dysregulated fatty acid metabolism and lipid excess causing insulin resistance in these insulin-sensitive tissues. Additional evidence in humans suggests that hepatic and skeletal muscle insulin resistance could occur concomitantly (Chen et al., 2015). It is therefore likely that the initial insult to cause whole body insulin resistance and diabetes could originate within different tissues.

Regardless of whether or not insulin resistance in muscle can cause type 2 diabetes, it is likely that insulin resistance is part of an overall metabolic inflexibility that also encompasses defects in fatty acid metabolism. From the cellular perspective, excess glucose entering and stored in the muscle cell in the absence of increased energy expenditure could be harmful. Is insulin resistance then an adaptive response? There are certainly physiological conditions in which insulin resistance develops, which is not pathobiology. Prolonged fasting induces skeletal muscle insulin resistance parallel to elevated fatty acid oxidation (Hoeks et al., 2010). Similarly, lipid overload, often used as a model for insulin resistance (Brehm et al., 2006; Itani, 2002; Yu, 2002), may represent a model of metabolic flexibility rather than revealing a pathological mechanism of insulin resistance. In support of this, Phelix et al. and Dube et al. demonstrated in independent studies (Dube et al., 2014; Phielix et al., 2012) that endurance-trained athletes who have a high oxidative capacity in muscle can increase fatty acid oxidation in response to lipid overload, but they preserve glycogen storage within muscle at the expense of decreasing glucose oxidation (Figure 1, **data obtained from (**Dube et al., 2014)). This enhanced metabolic flexibility was associated with a higher mitochondrial capacity in exercise-trained muscle (Dube et al., 2014; Phielix et al., 2012). Recent evidence also suggests that circadian variation in the molecular metabolic machinery can influence metabolic flexibility (Bass and Lazar, 2016). This is an emerging area of investigation that will help to clarify the role of insulin resistance and metabolic flexibility in human health and disease.

White adipose tissue orchestrates fuel flux

Compared to skeletal muscle, relatively little research is reported on metabolic flexibility of white adipose tissue (WAT). WAT has been historically regarded as a lipid reservoir; however, WAT is becoming increasingly recognized for playing an active role in lipid and glucose metabolism, as well as having the potential to increase thermogenesis (or ‘browning’) (Bostrom et al., 2012; Nedergaard and Cannon, 2014; Stanford et al., 2015). For purposes of this review, we focus on the inherent aspects of WAT metabolism and do not address the highly debated intricacies of WAT ‘browning’. WAT buffers circulating free fatty acids (FFAs) for peripheral tissues such as skeletal muscle and liver through a fine-tuned system of uptake, esterification and release of FFAs (so called triacylglycerol [TAG] cycling) (Reshef et al., 2003). This process requires – among many others – glycerol kinase, an

enzyme that was thought to be absent in adipocytes prior to a ground-breaking *in vitro* study in 2002 (Guan et al., 2002). It is worth noting that TAG cycling also occurs within brown adipose tissue (BAT) (Yu et al., 2002), but metabolic flexibility of BAT relates more to TAG cycling linked with combustion within the cell rather than with storage and supply for peripheral tissues as is the case for WAT. While absence (Reitman and Gavrilova, 2000) or excess (obesity) of WAT are both associated with metabolic complications, a normal weight healthy woman can have as much WAT as an obese man with type 2 diabetes (Jensen, 2002). The WAT mass *per se* is therefore not the only culprit in obesity-driven metabolic abnormalities, highlighting the importance of healthy and metabolically adaptable WAT. Likewise, it is pertinent to note that visceral and subcutaneous adipose depots are highly correlated in cross-sectional studies (Fox et al., 2007), which makes it difficult to disentangle their individual contributions to metabolic health. The primary focus of this review is on abdominal subcutaneous adipose tissue, largely due to pragmatic issues around tissue availability in humans, but we will address differences between these two depots where appropriate.

Substantial evidence implicates elevated FFA levels [from inappropriate lipolysis] as a significant etiological factor for insulin resistance and type 2 diabetes (Eckel et al., 2005; Frayn and Coppack, 1992; Frayn et al., 1996; Randle et al., 1963; Savage et al., 2007). More contemporary studies, however, have refuted the relationship between elevated circulating FFAs and obesity-driven insulin resistance. To summarize these findings, a recent systematic analysis by Frayn and colleagues compared over 2,000 overweight/obese individuals with non-obese controls and found that the average difference between those two cohorts was modest (in the range of 70 μmol/L) and unrelated to fat mass (Karpe et al., 2011). In humans, the only significant site of FFA liberation is abdominal subcutaneous (*i.e.,* upper-body) WAT with only a small and rather insignificant proportion arising from visceral adipose tissue (Nielsen et al., 2004). Transitioning from fasting to feeding elicits an insulin-stimulated suppression of lipolysis in WAT, a process that occurs via Akt-dependent and Akt-independent signaling pathways (Choi et al., 2010). In non-obese individuals, the EC_{50} of insulin to suppress lipolysis is half that required to suppress (hepatic) glucose output from the liver (Nurjhan et al., 1986). In the contrasting diabetic state, the amount of insulin required to completely suppress hepatic glucose production only achieves an 85% suppression of adipose lipolysis (Groop et al., 1989). These classical studies emphasize the sensitivity (and flexibility) of WAT to insulin in a healthy state and highlight its susceptibility to blunted insulin responsiveness as a potential early point of aberration in the etiology of whole body insulin resistance and type 2 diabetes.

Figure 2 captures the power of WAT metabolic adaptability to influence metabolism in other tissues such as skeletal muscle. A blunted suppression of lipolysis by insulin during a hyperinsulinemic-euglycemic clamp is associated with *reduced* glycolytic catabolism and metabolic flexibility in healthy people (2a) (Sparks et al., 2009), and segregates by diabetes status, rather than fat mass (2b) (unpublished data). Overnight fasting elicits high lipolytic activity in WAT for a robust supply of FFAs (Frayn et al., 1996) and commensurately high rates fat oxidation in skeletal muscle (low RQ), an ability that is blunted in individuals with a family history of type 2 diabetes (Ukropcova et al., 2007). In the context of the insulin sensitivity of WAT (EC_{50}) (Nurjhan et al., 1986), low levels of insulin are necessary for

WAT to meet this challenge of fasting-induced demand for FFAs. When oscillations of insulin secretion are attenuated and/or absent, such as in people with a family history of type 2 diabetes (Matthews, 1996; O'Rahilly et al., 1988), WAT may develop insulin resistance as an adaptive response or defense mechanism in order to continue supply of FFAs to skeletal muscle and other tissues as needed. Pathobiology is therefore difficult to determine without conditional context.

Considerable re-esterification of FFAs in WAT occurs during periods of active lipolysis such as fasting; in humans fasted for 60h, ~40% of liberated FFAs is recycled back into TAG in the subcutaneous WAT depot (Jensen et al., 2001), and the rest of the FFAs are released from WAT into circulation for catabolism by other tissues, typically skeletal muscle. WAT possesses a remarkable adaptability in obesity to expand and continuously store FFAs inertly as its innate function, which can often be perturbed in obesity-driven insulin resistance and results in down-regulation of basal (fasting) (Campbell et al., 1994; Horowitz et al., 1999) and dietary fat storage (McQuaid et al., 2011). Thiazolidinediones (TZDs) markedly improve insulin sensitivity and glucose homeostasis by expanding WAT (Girard, 2001) via a peroxisome proliferator-activated receptor (PPAR)-γ-induced rise in GyK levels and TAG cycling under conditions of fasting and feeding and eliminate reliance on glucose for such processes (Guan et al., 2002; Lehmann et al., 1995). Re-esterification is most prominent upon ingestion of a mixed meal when insulin induces the switch from FFA release to storage. Figure 3 elegantly illustrates the anabolic capacity of WAT. Over the course of three meals in a 24hr period, abdominally obese men have significantly lower transcapillary flux of FA (net fat storage and release) from WAT (McQuaid et al., 2011). Intuitively, as less dietary FFAs are progressively stored in WAT with each meal, these FFAs remain in circulation and are likely deposited ectopically in other tissues and lead to metabolic perturbations therein. Figure 4 depicts a progressive increase in post-meal RQ (so burning more carbohydrate than fat) by the 3rd of 3 meals over a 24hr period in lean healthy individuals (unpublished data). The essence of coordinated metabolic flexibility among tissues in the healthy state dictates that the more fat that is stored (and inertly sequestered) in WAT post-meal, the less fat that is available for catabolism by other tissues leading to more reliance on carbohydrate oxidation (higher RQ).

Rest to exercise – Fuel selection to support increased energy demand

Physical activity can dramatically increase energy expenditure and demand. Rigorous exercise can increase energy expenditure 25-fold compared to resting metabolic rate. The physiology and biochemistry of fuel selection during exercise has been the topic of investigation for several decades. The vast majority of human studies have been conducted in normal weight young subjects who typically have considerable metabolic flexibility in fuel selection. These concepts and efforts put forth to better understand fuel metabolism during exercise have also in large part been born out of the interest to improve sports performance. The literature is replete with studies aimed at strategies to prolong endurance by maintenance of higher rates of fatty acid oxidation (Jeukendrup et al., 1996; Jeukendrup et al., 1998a; Jeukendrup et al., 1998b; van Loon et al., 1999) and exogenous carbohydrate oxidation (Goodpaster et al., 1996; Horowitz et al., 1999) to preserve muscle glycogen stores, which has been demonstrated to limit performance.

Skeletal muscle accounts for more than 95% of energy requirements during moderate to vigorous exercise. Intramuscular glycogen, triglycerides, plasma glucose and plasma fatty acids (primarily from abdominal subcutaneous WAT lipolysis) combine to provide the necessary fuel to working muscle (Romijn, 1993). Thus exercise requires tremendous metabolic flexibility to increase energy supply from all of these sources to support the enormous energy demands of exercise primarily by skeletal muscle.

Many of the myocellular changes that occur during exercise, not surprisingly, are related to catabolism. Exercise is a powerful activator of AMPK (Jorgensen et al., 2006), which has been consistently reported to be a master energy sensor. Pharmacological activation of AMPK alters the expression of many of the same genes seen with exercise (Narkar et al., 2008). The sirtuin pathways have also been implicated in mechanisms of energy sensing in skeletal muscle and many other tissues requiring metabolic flexibility (Jing et al., 2011). Exercise acutely alters the molecular and biochemical machinery required to mobilize energy for carbohydrate and fatty acid oxidation. These changes in skeletal muscle promote greater energy supply. The metabolic flexibility to switch between glucose and fatty acid catabolism during acute exercise in healthy people is driven largely by the intensity and duration of exercise. Higher intensity exercise increasingly relies on glucose oxidation, through oxidative phosphorylation but more exclusively on anaerobic glycolysis during higher intensity exercise. This occurs independently of insulin (Goodyear and Kahn, 1998), as circulating insulin levels are normally very low during exercise. Fatty acid oxidation contributes quantitatively and proportionally less as exercise intensity increases (Brooks, 1997; Romijn, 1993). As exercise duration becomes longer, however, fatty acids make a greater contribution to overall energy supply (Jeukendrup, 2002).

One aspect of WAT metabolic flexibility is the ability to mobilize FFAs (primarily from abdominal subcutaneous WAT) in response to an acute exercise-mediated rise in catecholamines (Arner et al., 1990b). Visceral adipose tissue appears to be more responsive to adrenergic activation (Arner, 1995; Mauriege et al., 1987). Indeed, some studies have shown that the visceral (vs. subcutaneous) adipose depot has a greater relative change in response to exercise interventions (Schwartz et al., 1991; Thomas et al., 2000). The abdominal subcutaneous adipose depot is still considered the largest provider of plasma FFAs during an acute exercise bout with visceral providing a very small fraction since the visceral depot is much smaller in size (especially in the healthy state) (Horowitz, 2003). Even low-intensity exercise increases epinephrine concentration to about three-fold above basal (Henderson et al., 2007; McMurray et al., 1987). As the duration of fixed-intensity exercise increases, there is a rise in regional WAT lipolysis (Stallknecht et al., 2007; Stallknecht et al., 2001; Stich et al., 2000), which has been attributed to slow-acting hormones such as growth hormone (Divertie et al., 1991; Hansen et al., 2005; Healy et al., 2006). Selective blocking of β-adrenergic receptors in abdominal subcutaneous WAT during 30 minutes of moderate intensity exercise in lean individuals drastically reduces lipolysis during exercise (Arner et al., 1990b). To further illustrate this point, deletion of the key lipolytic enzyme adipose triglyceride lipase (ATGL) from adipocytes impairs acute exercise performance in mice due to reduced FFA supply to skeletal muscle (Dube et al., 2015), highlighting the critical need for WAT metabolic flexibility relative to other tissues. Deletion of ATGL from myotubes has no effect on exercise performance (Dube et al., 2015). Given

the reduction of β_2-adrenergic receptor density in adipocytes isolated from obese individuals (Arner et al., 1990a; Horowitz et al., 1999), it stands to reason that resistance to catecholamine action in WAT is one possible explanation for blunted fasting- and exercise-induced FFA release from WAT. The ability of WAT to liberate FFAs during acute bouts of exercise and over the course of repeated bouts of exercise (chronic training) plays an important role in supporting whole body fat oxidation, particularly in skeletal muscle.

In addition to increasing availability of fatty acids and glucose to energy production during activity, skeletal muscle also responds to acute exercise to prepare the organism for the next bout of activity. This, in many ways, precipitates an exercise-training response. These changes also pertain to catabolic processes, including autophagy (Mansueto et al., 2017) and other processes to promote organelle and cellular remodeling to enhance overall energy metabolism. Acute exercise induces epigenomic, transcriptomic and proteomic changes in skeletal muscle and WAT, which integrate changes in metabolic pathways to confer greater energy production and better metabolic flexibility for subsequent exercise bouts. Although the literature is extremely limited in this regard, chronic exercise augments methylation of CpG sites in genes related to lipogenesis and enriches expression of genes related with oxidative phosphorylation and protein synthesis in subcutaneous WAT of the leg (Ronn et al., 2013; Ronn et al., 2014). These recent studies highlight how the emergence and evolution of ‘omics’ technologies, and newer analytic methods, strategies and bioinformatics can be implemented to interrogate cellular changes in response to exercise.

Are some pathological conditions characterized by metabolic inflexibility during exercise?

Fuel selection during exercise in pathophysiological states such as obesity, insulin resistance and type 2 diabetes has received notably less attention. Despite having reduced fatty acid oxidation during resting, fasted conditions, subjects with obesity (Goodpaster et al., 2002; Horowitz and Klein, 2000) and type 2 diabetes (Colberg et al., 1996) have similar – or even elevated -- fatty acid oxidation during exercise. Moreover, patients with type 2 diabetes oxidize more plasma glucose during acute exercise (Colberg et al., 1996), which could help to explain part of the glucose lowering effects of exercise and activity in diabetes. Figure 4 highlights the ability to precisely and accurately quantify inter-individual differences as well as acute changes in human whole body fuel selection employing 24-hour whole-room calorimetry (unpublished data).

Few studies have investigated whether myocellular responses or changes during acute exercise vary according to aging, obesity or diabetes. Mandarino et al. reported that exercise-induced changes in gene expression are dependent upon skeletal muscle insulin sensitivity of the subject (McLean et al., 2015). *In vitro* studies could provide more mechanistic insight into acute exercise responses, since many of the metabolic phenotypes observed *in vivo* are preserved in culture in human satellite cells isolated from skeletal muscle (reviewed in (Aas et al., 2013)). For example, Ukropcova et al. demonstrated an intrinsic metabolic flexibility of human muscle cells in terms of suppressibility of glucose oxidation by fat (Randle effect) and adaptability of fat oxidation to increasing amounts of fat (high-fat feeding adaptability)

that were correlated with these same phenotypes observed *in vivo* of the donors (Ukropcova et al., 2005). Clearly, further study is needed to better understand the cellular changes that occur in muscle during – or in response to -- acute exercise, which could provide mechanistic basis for exercise improvements in health and disease. It stands to reason that primary human muscle cells could fill a gap in human clinical exercise trials and serve as a 'disease in a dish' model in which exercise mimetics (*eg*, electrical pulse stimulation, synthetic and naturally-occurring compounds) are utilized to dig deeper on molecular modifications, signaling pathways and mechanism-driven responses to exercise.

Effects of exercise training and calorie restriction-induced weight loss on metabolic flexibility

Exercise training induces changes in the epigenome, transcriptome and proteome to support increased storage of fuel and increased capacity for substrate utilization. In this sense, this anabolic flexibility supports improved metabolic flexibility. Exercise training can promote higher rates of fatty acid oxidation at rest and during acute exercise (van Loon et al., 1999). Exercise has the dual effect of enhancing insulin sensitivity (James et al., 1984), with the likely downstream benefits of reducing diabetes and cardiovascular disease risk. In a different context, the improved insulin sensitivity with exercise training enhances muscle glycogen storage (Sherman et al., 1981), which improves endurance exercise performance (Karlsson and Saltin, 1971). Several plausible mechanisms can explain improved insulin sensitivity and enhanced metabolic flexibility with exercise training. Increases in skeletal muscle mitochondrial biogenesis, mitochondria content and function have been reported to explain improvements in both insulin sensitivity (Coen et al., 2015a) and increased capacity for fatty acid oxidation (Jong-Yeon et al., 2002). Calorie restriction-induced weight loss also improves insulin sensitivity (Coen et al., 2015b), but in contrast to exercise, does not seem to enhance the capacity of skeletal muscle for fatty acid oxidation (Toledo and Goodpaster, 2013). Remarkably, these lack of improvements in fatty acid oxidation of skeletal muscle mitochondria correspond to the lack of response to weight loss (Coen et al., 2015a), although some studies have shown that calorie restriction increases mitochondrial content (Civitarese et al., 2007) and function (Vijgen et al., 2013).

Reducing fat mass via surgical removal (liposuction) of WAT does not produce metabolically beneficial results (Klein et al., 2004), pointing toward the need for a calorie-restriction-induced and/or an exercise-induced remodeling of WAT in order to achieve metabolic improvements within the adipose tissue. Little is known about the effects of exercise on metabolic flexibility (in terms of insulin and acute exercise bout responsiveness) and the related molecular mechanisms in WAT. Calorie-restriction-induced weight loss has a broader effect on the transcriptome in WAT compared with calorie restriction plus exercise (Lam et al., 2016). Additional studies are warranted to determine whether exercise training and weight loss may have common signatures that improve mitochondrial function, efficiency or reduce oxidative stress concomitant with enhanced metabolic flexibility.

Could metabolic flexibility be a target to prevent or treat disease?

Metabolic flexibility encompasses a variety of pathways and mechanisms. To the extent that one target could be engaged to alter fuel selection or energy expenditure, metabolic flexibility, or at least components of these, therefore, could be viable targets for therapy. Enormous efforts have been made to alter metabolic flexibility in obesity and diabetes. A key controversy in this area is whether alterations in fuel selection without concomitant increases in energy demand will prove to be therapeutic in the face of nutrient overload or obesity (see review by Muoio (Muoio, 2014). For example, increasing mitochondrial fatty acid flux and oxidation may (Bruce et al., 2009) or may not (Koves et al., 2008) improve insulin resistance. Neither strategy, however, increases energy expenditure or demand (like exercise). Simply put, while strategies to alter substrate metabolism or metabolic flexibility could impact obesity and metabolic disease in the context of nutrient overload, without a concomitant increase in energy demand, they do not represent a true exercise mimetic.

There are also several examples in oncology whereby drugs are targeted to tumor metabolism have anti-tumorigenic effects (Chaube et al., 2015). Insulin sensitizers have been shown to be reasonably effective for treatment of type 2 diabetes (Eldor et al., 2013). Drugs that affect fatty acid oxidation, including PPAR agonists (Sahebkar et al., 2014), ACC inhibitors (Bourbeau and Bartberger, 2015), have been developed to affect fuel metabolism in obesity, diabetes and heart disease. AMPK activators (AICAR, Methotrexate, Metformin) have also shown promising results in targeting metabolic flexibility to treat metabolic disease (Hardie, 2013; Zhang et al., 2009). Interestingly, some of these compounds have been developed and touted as exercise mimetics. Given that exercise profoundly affects metabolic flexibility, similar strategies to improve both metabolic flexibility and sports performance have been employed. Perhaps the most notable recent example of this has been the documented and well-publicized use of Melondrate, which has been used by some countries (not approved in the U.S.) to inhibit fatty acid oxidation through decreases in carnitine palmitoyl transferase (CPT), in order to treat cardiac dysfunction and impaired cardiac metabolism (Arduini and Zammit, 2016). However, there has been little documentation of any performance benefit using this compound, despite its clear effect on energy or fuel utilization. Any pharmacologic strategy purporting to mimic exercise would need to impact metabolic flexibility and also induce increases in energy expenditure and demand similar to exercise. This should prove to be challenging if not impossible. In summary, targeting energy metabolism without unwanted negative side effects has proven to be extremely difficult in practice.

Concluding Remarks

The broad concepts of metabolic flexibility have prompted decades of investigation into factors and mechanisms influencing energy availability and fuel selection. Much of the early work focused on understanding insulin resistance in skeletal muscle and adipose tissues as part of an overall metabolic inflexibility. More recent studies have investigated metabolic flexibility within muscle and adipose cells, and their respective roles in overall metabolic flexibility. Studies employing fasting to feeding (or insulin stimulation), rest to exercise, or exercise training interventions with adipose and muscle biopsies have revealed important

mechanistic clues underpinning metabolic flexibility in humans as summarized in Figure 5. Efforts should be continued to interrogate mechanisms and potential treatments for insulin resistance and metabolic inflexibility, including the capacity for fatty acid oxidation, underlying obesity, type 2 diabetes and related conditions.

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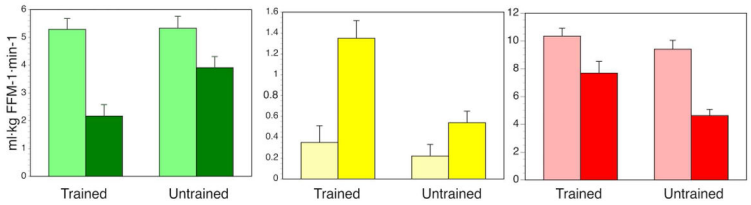

Figure 1. Acute lipid oversupply during hyperinsulinemia reveals metabolic flexibility in trained compared to untrained subjects

During a hyperinsulinemic-euglycemic “glucose” clamp without (light bars) or with (dark bars) co-infusion of intralipid, trained subjects decrease glucose oxidation (green bars), increase fatty acid oxidation (yellow bars) and preserve muscle glycogen storage (red bars) relative to untrained subjects, who exhibit metabolic *inflexibility*. In other words, untrained subjects do not effectively decrease glucose oxidation or increase fatty acid oxidation, and they have diminished glycogen storage in the face of lipid overload. Data were obtained from (Dube et al., 2014).

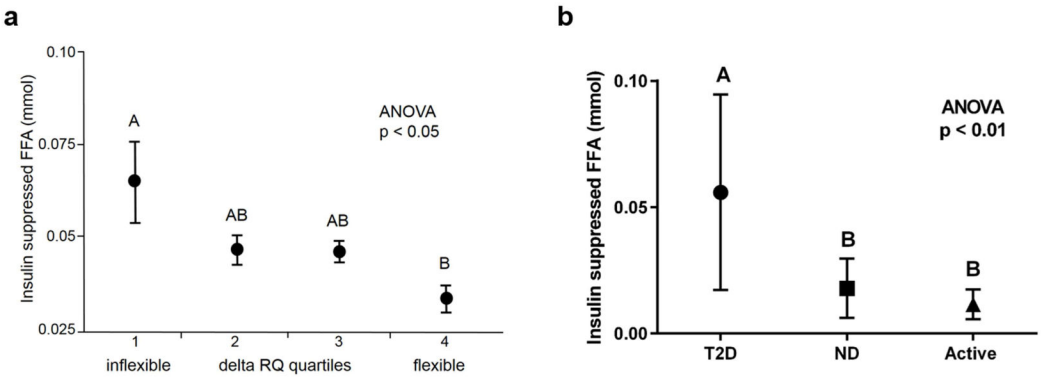

Figure 2. Adipose tissue insulin responsiveness is critical for metabolic flexibility of other organs and is blunted in diabetes

(a) Free fatty acids (FFAs) during a during a hyperinsulinemic-euglycemic clamp with a primed-continuous insulin infusion of 80 mU/m^2/min for 3–4 hours are related to reduced metabolic flexibility (delta RQ) in a population of 56 healthy young men subdivided into quartiles of metabolic flexibility. **(b)** People with type 2 diabetes (T2D; n=18) have significantly higher levels of FFAs during an hyperinsulinemic-euglycemic clamp with a primed-continuous insulin infusion of 100 mU/m^2/min for 3–4 hours compared with age- and BMI-matched healthy people (ND; n=6) and highly active people (Active; n=8). ANOVA was used to test for differences across quartiles of metabolic flexibility (delta RQ), with post hoc testing by mean equality contrast between different groups using the Tukey–Kramer HSD; alpha = 0.05. Type I error rate was set a priori at $p < 0.05$. Data are shown as means ± SEM. Levels which do not share the same letter are significantly different. FFAs were measured by high-performance liquid chromatography (HPLC) for **(a)** and by enzyme assay for **(b)**.

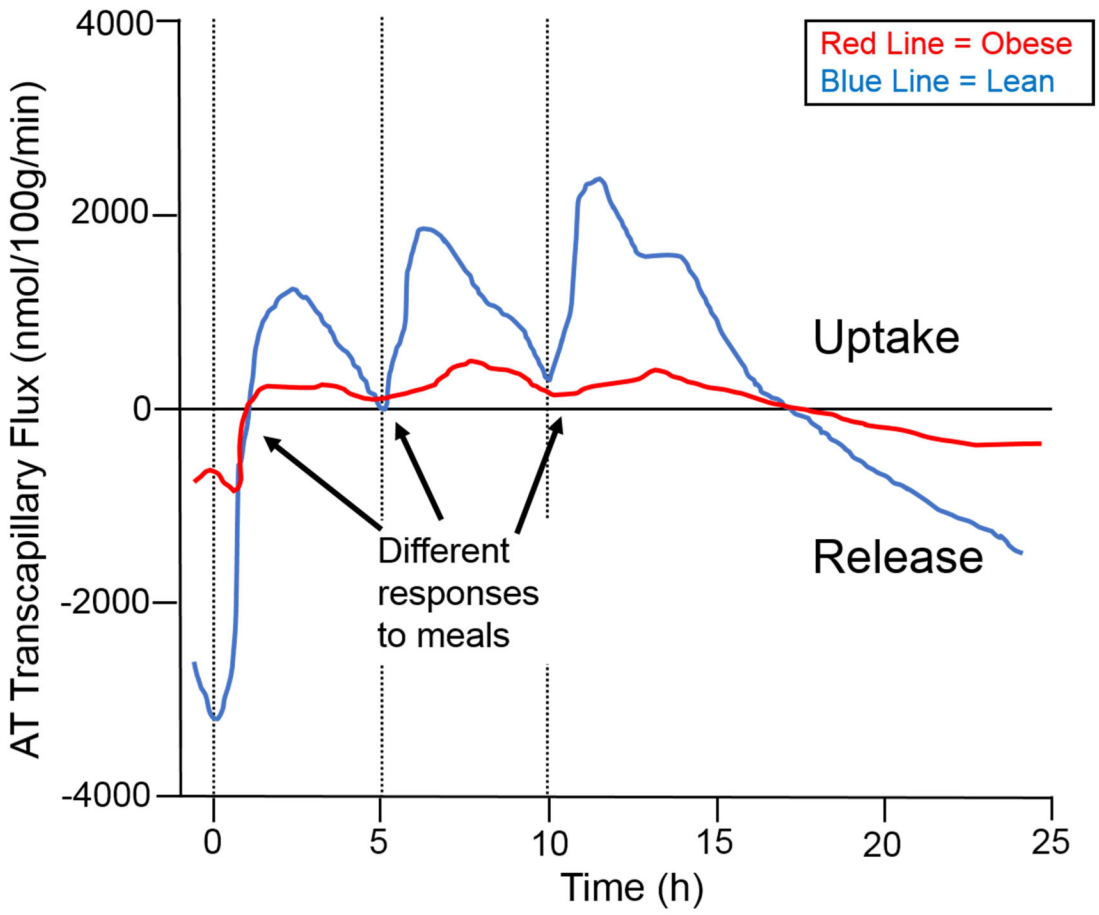

Figure 3. Transcapillary flux of FFAs is reduced with obesity

The release of free fatty acids (FFAs) and the extraction of triglycerides from plasma (nmol/100g/min) in abdominal subcutaneous white adipose tissue (WAT) is significantly lower in the WAT of abdominally obese men (red line) compared with lean men (blue line) (both time x group, $p < 0.001$) across consumption of three mixed meals over the course of 24 hours. Meal consumption is indicated by a dashed line.

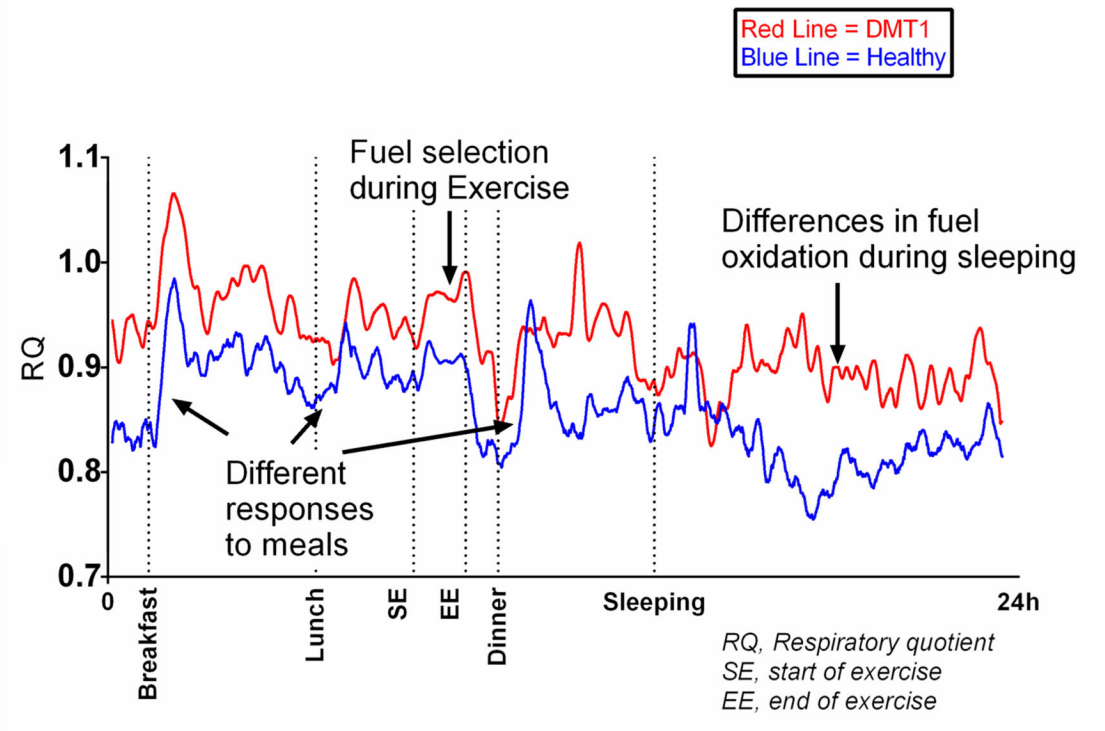

Figure 4. Respiratory quotient (RQ) kinetic during 24 hours in a metabolic chamber

Lines represent individual responses for a type I diabetes mellitus patient (DMT1, red line) and a healthy volunteer (blue line). Arrows indicate different features of metabolic flexibility (exercise, response to a meal and sleeping) as assessed in whole room respiratory chamber.

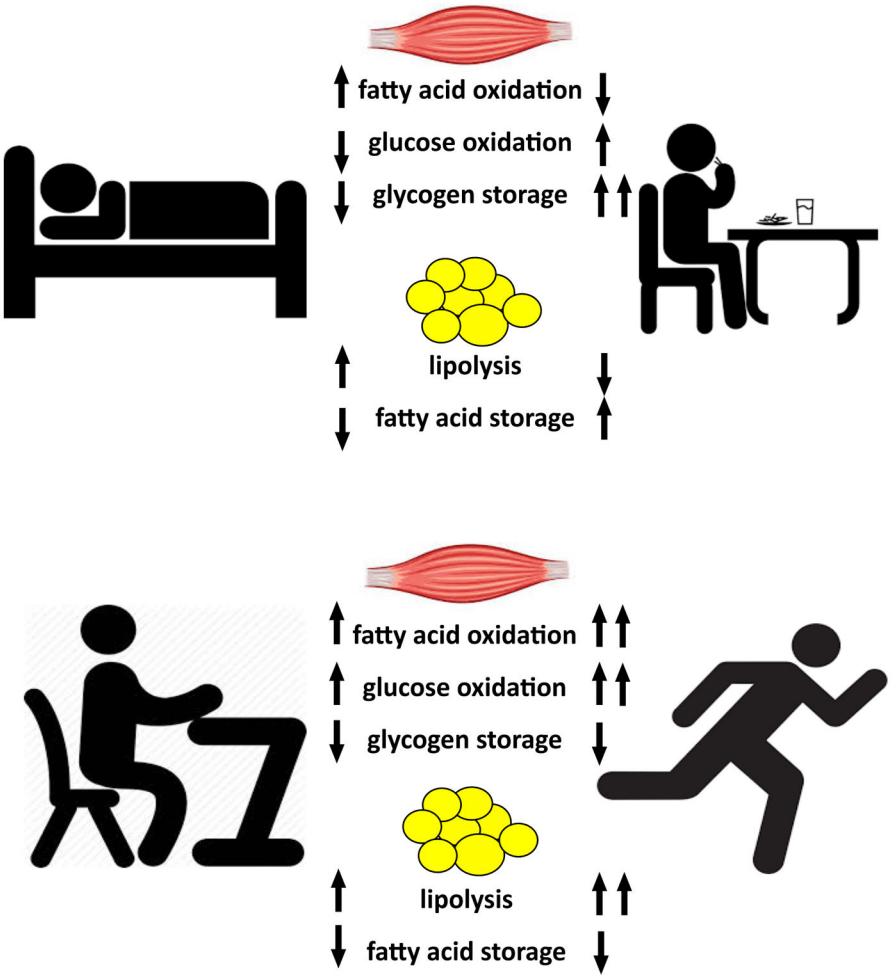

Figure 5. Summary of fuel metabolism changes within skeletal muscle and adipose tissue during periods of sleeping, fasting, feeding, rest and exercise

Skeletal muscle switches from higher rates of fatty acid oxidation during sleeping/post-absorptive conditions to greater oxidation and storage of glucose after feeding, and reduced fatty acid oxidation. Adipose tissue shifts from higher rates of lipolysis to suppression of lipolysis and fat storage during the fasting to feeding transition. From rest to exercise, skeletal muscle increases rates of both fatty acid and glucose oxidation to support higher energy demands, while lipolysis in adipose tissue is drastically enhanced.