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Metabolic Reserve of the Heart: The Forgotten Link Between Contraction and Coronary Flow

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Cardiovascular research owes much to Ed Sonnenblick. Few would dispute that his understanding of the cellular basis of cardiac function have ushered in a new era of heart research, the era of the heart muscle cell.^{1,2} In the course of his work Ed had more than a passing interest in cardiac energetics, although he never ventured in the complexities of intermediary metabolism.^{3,4} If he had done so he would have enjoyed the logic of metabolic regulation as much as he enjoyed the logic of the organization of the sarcomere.^{5,6,7} In the following we have made an attempt to review metabolic aspects of energy transfer in the heart with a focus on the regulation of energy substrate metabolism in response to stress- the metabolic reserve of the heart.

A few principal comments are in order. The heart converts chemical energy present in the form of substrates and oxygen to mechanical energy (measured as cardiac work) and heat (measured as calories).⁸ An abrupt increase in cardiac work results in the recruitment of reserves in contractility and coronary flow.^{9,10} In clinical practice the coronary flow reserve is used to quantitate the capacity of the coronary circulation,¹¹ while contractile reserve is used to quantitate the response of the heart muscle to inotropic stimulation.¹² Missing in this equation is the heart's metabolic reserve which cannot be assessed as readily as coronary flow reserve and contractile reserve. However we argue that increases in contractility are coupled to increases in cardiac metabolism and form an integral part of cardiac function. In contrast to contractile function, the metabolic function is, however, very difficult to assess.

We have previously proposed that metabolism (in the form of metabolic signals) provides the link between contraction and gene expression.¹³ We now propose that metabolism forms a link between contractile reserve and coronary flow reserve (Figure 1). The metabolic reserve, called up by an acute increase in work load of the heart, involves the mobilization of glycogen, a switch of substrate oxidation from fat to carbohydrates and the capacity to increase oxidative metabolism of energy providing substrates. We will explore the notion

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that impairment of the metabolic reserve results in contractile dysfunction of the stressed heart, while restoration of the metabolic reserve restores contractile function.

Muscle as a model for contractile and metabolic adaptation and maladaptation

Contractile Adaptation: Resting and Running

In order to understand the concept of metabolic reserve in heart muscle it helps to examine analogies provided by the physiology of skeletal muscle. Here we follow Ed Sonnenblick's reasoning and experimental strategy: His dictum was that "a muscle is a muscle". In the transition from rest to exercise the skeletal muscle mobilizes its energy stores in order to meet increased demands. There are no reserves of ATP in muscle. Instead, energy is stored in muscle in three forms (Table 1). The first is phosphocreatine which can rapidly donate its high energy phosphates to produce ATP from ADP. Energy available from phosphocreatine (PCr) is relatively modest, although it has been estimated that PCr can contribute about half of the amount of energy expended during a 100 meter sprint race.^{14,15} However, when energy requirements are sustained, PCr is used only during very rapid bursts of exercise¹⁶ and the muscles have to rely on aerobic metabolism of the other two major stores. The second endogenous form of energy is glycogen. Glycogen provides 16 kilojoules (KJ) of energy per gram (g) oxidized (Table 1).¹⁷

Because glycogen is stored along with hydration water, the muscle's storage capacity for glycogen is limited. However, glycogen has the advantage that it consumes much less oxygen compared to fatty acids for the same amount of energy converted to mechanical work. In addition, the rapid activation of phosphorylase¹⁸ assures that glycogen stores are readily available for use as fuel in muscle. The third form of stored energy is represented by triglycerides. Triglycerides are slowly mobilized and provide 35 KJ of energy per gram oxidized¹⁷. Most of the body's energy stores consist of triglycerides in adipose tissue. Their oxidation is less efficient compared to glycogen, both in terms of the amount of oxygen required and in terms of the rate of energy conversion (power output). (Figure 2).¹⁹ In short in the absence of a "universal fuel" the body behaves like a hybrid engine and switches between fuels depending on fuel supply, hormone levels and the nature as well as the duration of stress (exercise). For instance athletes running long distances rely first on the aerobic metabolism of glycogen. After a short while glycogen stores are depleted and muscle oxidizes triglycerides.^{20,21} It has been shown that in marathon runners 10–50% of the energy required is provided by fatty acid oxidation.¹⁴ Elite marathon runners use triglycerides at the lower end of this range because triglycerides and fatty acids are a less efficient source compared to glycogen. In other words one of the training goals in marathon runners is the increase of glycogen stores²² in their skeletal muscles along with up-regulation of the enzymes of the metabolic pathways which contribute to glycogen oxidation.²³ After the exercise, oxygen consumption remains high (excess post exercise oxygen consumption, EPOC) in order to repair the "damages" incurred by exercise. At this time the rate of fatty acid oxidation increases and the glycogen stores of the muscles are replenished with the use of carbohydrates.^{24,25} As it will be shown below, these principles of muscle metabolism also apply to the heart.

Metabolic Adaptation of the Heart

Response to Increased Energy Demand—To reiterate upon increased energy demand the muscles initially rely on carbohydrate oxidation. What are the mechanisms for enhanced carbohydrate oxidation with exercise? Observations first made in skeletal muscle of animals provide a conceptual framework for mechanisms of enhanced carbohydrate metabolism.

The transport of glucose in the muscle is enhanced. This is related to increased levels in the glucose transporter GLUT4 mRNA and GLUT4 protein, for instance in exercising rats.²⁶ As shown in Figure 3 this can happen through receptor dependent and receptor independent mechanisms. Besides contractile activity glucose transport activity is stimulated by insulin or hypoxia and ischemia and is increased roughly in proportion to the adaptive increase in GLUT4 protein in epitrochlearis muscles. When epitrochlearis muscle is incubated in a medium containing glucose and insulin, glycogen accumulation over 3 h is twice as great in muscles of rats that exercised as in control muscles,²⁷ suggesting that a rapid increase in GLUT4 expression is an early adaptive response of skeletal muscle to exercise and that the physiological role of this adaptation is to enhance the replenishment of muscle glycogen stores. From the same group came evidence that glycogen supercompensation masks the effect of a training induced increase in GLUT-4 on muscle glucose transport²⁸ and that prevention of glycogen supercompensation prolongs the increase in muscle GLUT4 after exercise.²⁹ It is tempting to speculate that this adaptive mechanism helps restore glycogen in the “fight and flight” response. At the same time, a reversal of the exercise-induced increase in GLUT4 in response to carbohydrate feeding and glycogen supercompensation, probably prevents excessive glycogen accumulation, as observed in certain inborn errors of metabolism (Pompe’s disease, von Gierke’s disease). Glycogen content in muscle does not affect GLUT 4 alone. The transcriptional activation of metabolic genes in response to exercise is blunted when pre-exercise muscle glycogen content is high, whereas transcriptional activation is enhanced when pre-exercise muscle glycogen content is low. This raises the possibility that signalling mechanisms regulating exercise-responsive genes may be sensitive to muscle glycogen content.³⁰ When glycogen content is high, muscle preferentially uses glycogen as a source of energy due to its higher efficiency as a fuel. Conversely when glycogen stores are low, skeletal muscle fatty acid oxidation and mitochondrial biogenesis are induced.³¹ This induction can be prevented by a high carbohydrate diet during recovery.³² The findings support the hypothesis that factors associated with substrate availability and/or cellular metabolic recovery (muscle glycogen restoration) influence the transcriptional regulation of metabolic genes in skeletal muscle of humans during recovery from exercise. The control of metabolism in recovery by glycogen levels underlines its importance as the metabolic reserve of the muscles.

Response to Altered Metabolic Environment (Exercise, Starvation, Diabetes)

—Exercise, starvation and diabetes are three physiological states characterized by increased blood levels of free fatty acids (FFA).³³ The surplus of FFAs leads to activation of the enzymes of beta oxidation.³⁴ This is coordinated by the increase of peroxisome proliferator activated receptor alpha (PPAR- α).³⁵ In this context skeletal muscle uses the substrate that is available in the specific environment. This adaptation offers two significant advantages. First it supports the muscle’s metabolic needs and second avoids the accumulation of metabolic byproducts that could be harmful to the muscle.

Metabolic Maladaptation

We will use the example of diabetes and heart failure to assess metabolic maladaptation of skeletal muscle as it also applies to the heart. Overexpression and overactivity of Glycogen Synthase Kinase 3 (GSK-3) in skeletal muscle of rodent models of obesity and obese type 2 diabetic humans are associated with an impaired ability of insulin to activate glucose disposal and glycogen synthase (GS).³⁶ In skeletal muscle of prediabetic obese Zucker rats chronic selective GSK-3 inhibition significantly improves insulin receptor substrate -1 (IRS-1) signaling and enhances insulin stimulated glucose transport.³⁷ Increased cell surface GLUT 4 protein has also been documented in Zucker diabetic fatty rats.³⁸ The overexpression of carnitine palmitoyltransferase I (CPT I) (a key enzyme of fatty acid oxidation) normalizes insulin-stimulated glucose metabolism in muscle cells pretreated with

palmitate. Those cells also seem to be protected against the palmitate induced accumulation of diacylglycerol and ceramide, and PKC theta and zeta activation, all of which are signaling molecules of insulin resistance.³⁹ Overexpression of liver CPT I also increases insulin-stimulated incorporation of glucose into glycogen and deoxyglucose uptake in palmitate-treated cells. In the latter study, however, the insulin sensitizing effect was independent of changes in intracellular lipid content.⁴⁰ Another pathway that seems to be involved in this process is that of AMP kinase (AMPK). AMPK activity in skeletal and cardiac muscle results in increased rates of glucose transport and may play a role in enhancing muscle and whole body insulin sensitivity for glucose transport under conditions such as exercise.⁴¹ The mechanisms for AMPK-mediated glucose transport involve proximal signals that are distinct from that of insulin (Figure 3).

In this context it is of interest that patients with congestive heart failure (CHF) develop impaired insulin-stimulated whole-body glucose uptake, despite normal insulin signalling in skeletal muscle at the level of IRS-1, PI-3 kinase or Akt. Thus, insulin signalling defects are not a primary cause of impaired whole-body insulin-mediated glucose uptake in CHF. In the same vein exercise training is beneficial to treat the metabolic abnormalities associated with CHF and improves insulin action on whole-body glucose uptake independent of enhanced insulin signal transduction. Thus, altered insulin action on glucose uptake in CHF patients occurs at a distal component of the insulin signal transduction pathway regulating glucose uptake.⁴² Patients with heart failure due to coronary artery disease are insulin resistant; this insulin resistance affects both the myocardium and the skeletal muscle and is independent of blood flow.⁴³ Type 2 diabetes mellitus confers a greater degree of myocardial insulin resistance to those patients.⁴⁴ Reduced suppression of circulating free fatty acids (rather than further reduction of myocardial GLUT 4 levels) seems to limit myocardial glucose utilization in the diabetic patients with CHF due to coronary artery disease.⁴⁴ It is important to note that a direct relation between myocardial glucose uptake (measure of insulin resistance) and left ventricular ejection fraction (measure of contractile reserve) has been documented in the literature.⁴⁵

Contractile and Metabolic Reserve of the Heart

Glucose, Lactate, Glycogen

Nature has endowed the heart with a huge potential for ATP generation. Nature also prevents the heart from generating ATP unless it needs ATP and uses it!⁴⁶ During an acute increase in heart work, induced by stimulation with epinephrine and an increase in afterload, rates of oleate and triglyceride oxidation remain unchanged (Figure 4). Instead, the rate of glycogen oxidation increases instantly and then transiently. At the same time the oxidation of glucose and lactate increases more gradually and remains elevated throughout the stimulation.⁴⁷ With prolonged inotropic stimulation, glycogen levels are restored. Glycogen synthesis results from activation of GS, which in turn is regulated by a series of complex reaction sequences.⁴⁸ The importance of glycogen as the energy reserve of the heart can be demonstrated by another experiment. During an acute low to high work transition of the rat heart improved homeostasis is demonstrated at the metabolic milieu of exercise (increased lactate due to increased skeletal muscle glycolysis and increased free fatty acids due to adrenergic stimulation of lipolysis in adipose tissue). The improved homeostasis is manifested by attenuation of net glycogenolysis.²⁷ The glycogen sparing is partly explained by *de novo* glycogen synthesis during or immediately following glycogen breakdown. In the cardiomyocyte, the allosteric activator of glycogen synthase, glucose-6-phosphate, is elevated in the metabolic milieu of exercise. In a practical setting it has been shown that marathon and ultramarathon runners start replenishing their skeletal muscle glycogen stores even during the time of the race.^{14,22}

GSK-3 which phosphorylates and inactivates GS, has been implicated in the regulation of multiple physiologic processes in the heart and skeletal muscle, including glycogen turnover and cell growth (Figure 3). In metabolic terms inhibition of GSK-3 results in activation of GS as well as basal and insulin stimulated increase in glucose uptake of skeletal muscle without increasing the total protein content of glucose transporters GLUT1 and GLUT4.⁴⁹ Bouts of submaximal and maximal exercise activate the serine- threonine kinase Akt and decrease GSK-3a activity, both in humans and rats.⁵⁰ Contractile activity is also partly responsible for the activation of Akt.⁵¹ In Akt over-expressing transgenic mice left ventricular contractile function is increased at baseline compared to wild type mice.⁵² With increasing concentrations of dobutamine contractility became the same in both groups. Because transgenic mice started from a hypercontractile state the relative increase in contractile performance was less in Akt over-expressing hearts than in wild types. [39] Akt increases cardiac size and contractility under resting conditions, while it phosphorylates and deactivates GSK -3. When phosphorylated, GSK-3 inhibits GS phosphorylation. When dephosphorylated, GS promotes glycogen synthesis (Figure 3). The essence of this complex signaling sequence is the build-up of metabolic reserve that is readily mobilized in times of need.

Fatty Acids, Ketone Bodies, Triglycerides

The regulation of long chain fatty acid metabolism in response to acute increase in cardiac work is equally complex (Figure 5). In contrast to glucose metabolism fatty acid metabolism is regulated predominantly at the transcriptional level and through feed-forward mechanisms. For example exercise raises free fatty acid levels in the blood.³³ Most likely as a result of ligand activation the content of PPAR- α and its family of target proteins that regulate fatty acid oxidation [medium-chain and very long chain acyl-CoA dehydrogenase (MCAD and VLCAD)] are doubled with endurance training in skeletal muscle.⁵³ Indeed, exercise increases transcription and/or mRNA content of pyruvate dehydrogenase kinase 4 (PDK4), uncoupling protein 3, lipoprotein lipase, CPT I, hexokinase II, peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1 α), and PPAR- α .³¹ Endurance exercise also increases PGC-1 α and the nuclear respiratory factors 1 and 2^{54,55} which have been shown to promote mitochondrial biogenesis.⁵⁶

Coupled Metabolic and Contractile Reserve of the Heart in the Perinatal Period

The fetal heart is an excellent example for the concept of a cardio-metabolic reserve. It operates in a hypoxic environment and oxidizes lactate and glucose⁵⁷, while its ability to oxidize long chain fatty acids is limited.⁵⁸ Commensurate with augmented carbohydrate metabolism is the prominence of glycogen in the fetal heart. Glycogen occupies more than 30% of the cell volume in fetal cardiomyocyte⁵⁹, and fetal mitochondria are incompletely developed.⁶⁰ In spite of the hypoxic environment cardiac output is normal in the fetal heart.⁶¹ Collectively, the metabolic features of the fetal heart prepare the organism with the stress of birth. Birth is the ultimate challenge for the cardio-metabolic reserve of the heart. The accumulation of glycogen (metabolic reserve) in the fetal heart is a mechanism for the heart to deal with the increased energy demands. Abnormal cardiac development and function can be demonstrated in mice which lack heart glycogen due to disruption of the GYS1 gene which encodes GS.⁶²

Immediately after birth glycolysis remains the predominant source of energy.⁶³ Shortly afterwards, however, there is a shift from glucose and lactate oxidation to fatty acid oxidation. This energy metabolic switch is paralleled by changes in the expression of the enzymes involved in the respective metabolic pathways.⁶⁴ Recent evidence indicates that

this postnatal gene regulatory effect involves the actions of the nuclear receptor PPAR α and its coactivator (PGC-1 α).⁵⁶ PGC-1 α promotes mitochondrial biogenesis and the activation of PPAR- α leads to the increase of muscle CPT I. The latter is also an effect of the reduction in malonyl CoA in the newborn heart.⁶⁵ This switch to free fatty acid oxidation ultimately serves better the energy needs in the postnatal heart. With hypertrophy, atrophy and heart failure⁶⁶⁻⁶⁸ the heart reverts to predominant glucose metabolism and re-expresses the fetal gene pattern. The DNA binding activities and nuclear expression of repressors like Sp1/3 and the chicken ovalbumin upstream promoter transcription factor (COUP-TF) in normal fetal mouse heart are similar to those in the hypertrophied adult heart.⁶⁶ These results identify a transcriptional regulatory mechanism involved in the re-induction of a fetal metabolic program during different disease states of the myocardium. This may be teleologically related to the better energy efficiency of glucose oxidation that preserves contractile function during those disease states, as we will see below.

Impaired Contractile and Metabolic Reserve of the Diseased Heart

Hypertrophy - Atrophy

Pressure overload (i.e. consequent to hypertension, or aortic stenosis) leads to left ventricular hypertrophy. The structural changes are preceded by changes in the metabolic machinery of the heart.⁶⁹ Even before there is any evidence of cardiac hypertrophy in hearts from hypertensive rabbits the rates of glucose utilization are increased and rates of ketone body utilization are decreased. Activities of key enzymes of carbohydrate metabolism (phosphorylase, hexokinase, phosphofructokinase, and lactate dehydrogenase) are increased, while those of ketone body metabolism (3-oxoacid-CoA transferase, acetoacetyl-CoA synthase) are decreased and those of the citric acid cycle (citrate synthase, 2-oxoglutarate dehydrogenase) are not different between groups. In an experimental model of right ventricular pressure overload the expression of genes involved in the thioesterification, mitochondrial import, and beta-oxidation of fatty acids are coordinately down-regulated.⁶⁶ Studies of the gene encoding human MCAD, which catalyzes a rate-limiting step in the FAO cycle, confirm that repression of MCAD gene expression in the hypertrophied ventricle occurs at the transcriptional level.⁶⁶ The master-switch in all of those changes is the PPAR- α ⁷⁰ together with the coactivator PGC-1 α .^{71,72} During cardiac hypertrophy the activity and gene expression of PPAR- α are both downregulated. The rapid decline in PPAR- α activity is thought to be due to its phosphorylation by extracellular signal-regulated kinase (ERK),⁷³ a member of the mitogen activated protein kinases (MAPK) family which is involved in the cardiac growth signaling. At the same time transcriptional repressors, like the (COUP-TF)/erbA-related protein 3 and Sp1 and Sp3 proteins, interact with the pressure overload responsive unit.⁶⁶ COUP-TF is known to repress the transcriptional activity of the MCAD promoter leading in decreased fatty acid oxidation.⁷⁴

Another signaling pathway of cardiac growth is the pathway of serine-threonine kinase Akt.⁷⁵ Specifically Fas ligand induces Akt and GSK3 β phosphorylation in cardiomyocytes.⁷⁶ Phosphorylation leads to inactivation of GSK3 β (see above). GSK3 β is considered a negative regulator of cardiac hypertrophy.^{77,78} In this way induction of Akt leads to cardiac hypertrophy. It has also been shown that induction of Akt leads to prevention of apoptosis and regulation of glucose metabolism.⁷⁹ As already discussed, the inactivation of GSK3 β also leads to increased glycogen synthesis.⁸⁰ Thus the GSK3 β pathway regulates both cardiac glycogen metabolism and cardiac growth. The expression of GSK 3 β in the postnatal cardiomyocyte leads to impairment in growth and contractile function due to down-regulation of the sarcoplasmic reticulum calcium ATPase (SERCA2 α) by GSK-3 β .⁷⁸

The hypertrophy and subsequent metabolic switch to glucose oxidation may be an adaptive mechanism. In a model of PPAR- α deficient hearts, which mimics the hypertrophied heart, the substrate switch from fatty acid to glucose and lactate is sufficient to sustain normal energy metabolism and contractile function at rest.⁸¹ As already mentioned Akt induction leads to hypertrophy with preserved contractile function and cardioprotection after ischemia and reperfusion.⁸² Also the myosin isoform MHC- β is upregulated during cardiac hypertrophy. The decreased contractile velocity of MHC- β is associated with greater economy in force generation, improving myocardial efficiency.⁸³ The switch in sarcomeric proteins may be induced by glucose regulated transcription factors like Sp1 providing another evidence of the tight link of metabolic and contractile reserve in the heart.^{84,85}

Decreased ATP synthesis (measured by 31P magnetization transfer) during high workload in the PPAR- α deficient hearts which mimic hypertrophy though results in progressive depletion of the metabolic reserve (i.e., inability to increase glucose and lactate oxidation from baseline) and failure to sustain high contractile performance. Interestingly, the metabolic and functional defects in PPAR- α (-/-) hearts can be corrected by over-expressing the insulin-independent glucose transporter GLUT1, which increased the capacity for glucose utilization beyond the intrinsic response to PPAR- α deficiency. It does so partly by increasing the glycogen content of the heart.⁸¹ Finally PPAR- α reactivation in hypertrophied hearts blocks skeletal α -actin induction, reverses the down-regulation of measured PPAR- α regulated genes, and prevents substrate switching. This PPAR- α reactivation concomitantly results in severe depression of cardiac power and efficiency in the hypertrophied heart measured *ex vivo*.⁸⁶ Thus, PPAR- α down-regulation and a metabolic switch are essential for the maintenance of contractile function of the hypertrophied heart, at least during rest. Furthermore pharmacologically induced regression of pressure-overload cardiac hypertrophy normalizes glucose metabolism as well as left ventricular function during reperfusion.⁸⁷ In the atrophied heart a similar down-regulation of PPAR- α and PPAR- α regulated genes along with induction of the fetal gene program has been documented.^{88,89}

Ischemia

A decrease in oxygen delivery to the myocardium results in down-regulation of oxidative metabolism and reduced contractile function. It seems that the acute switch from aerobic to anaerobic metabolism is necessary for immediate cell survival. This switch is achieved by a change-over from fatty acid to glucose and lactate oxidation. Over the long-term hypoxia inducible factor 1a (HIF-1a) is responsible for the transcriptional up-regulation of glucose transporter 1 and various glycolytic enzymes.⁹⁰ In cultures of myocardial cells hypoxia reduces PPAR- α /RXR binding activity at the promoter region (fatty acid responsive element 1 FARE-1) of the muscle CPT-I gene which encodes the enzyme responsible for the rate limiting step in fatty acid oxidation.⁹¹ It does so by diminishing the availability of retinoid X receptor (RXR) which forms a heterodimer with PPAR- α , necessary for the PPAR- α 's metabolic actions. In vivo hypoxia decreases transcript levels of PPAR- α and PPAR- α regulated genes (PDK4, mCPT-I, and malonyl-CoA decarboxylase (MCD) mRNA levels) resulting in decreased fatty acid oxidation and increased reliance of the heart on glucose.⁹² Hypoxia induces changes in myosin heavy chains isoforms in myocardial cells *in vivo* and *in vitro*.⁹³ Specifically a shift from MHC α to the more oxygen efficient MHC β is noted. This transcriptional adaptation may be part of a program that preserves cardiac function during decreased oxygen supply.

In perfused rat hearts, preconditioning increases phosphorylation of GSK-3 β , a downstream target of PI3-kinase and protein kinase B (PKB). This leads to inactivation of GSK-3 β . Inhibition of GSK-3 β results in improved post-ischemic function and reduced infarct size after preconditioning.⁹⁴ These findings indicate that inhibition of GSK-3 β is protective and

that this PI3-kinase-dependent signaling pathway may play an important role in ischemic preconditioning. Another study shows that erythropoietin and preconditioning lead to additive infarct size-limiting effects by additive phosphorylation of GSK-3 β at the time of reperfusion by Akt-dependent and -independent mechanisms.⁹⁵ Akt over-expression has been shown to decrease infarct size after ischemia.⁸² It is important to notice that GSK-3 β inhibition also leads to increased glycogen synthase activity. It may be that preservation of metabolic reserve (i.e., glycogen) results in improved post-ischemic function.

Persistent stunning can be induced regionally by repetitive episodes of ischemia and full reperfusion. After repeated episodes of ischemia and reperfusion myocardial function does not decrease further despite a similar reduction in coronary blood flow as with the first episode. So repetitive ischemia- reperfusion leads to a stable reduced contractile function.⁹⁶ At the same time an increase in glucose uptake and decrease in free fatty acid uptake is noted. The mechanism behind it may be a reduction in PPAR- α regulated genes.⁹⁷ Studies reveal enhanced glycogen deposition in those areas, which can be explained by decreased GSK-3 protein levels and activity. These results indicate that persistent stunning, even in the absence of chronic ischemia, can mimic the phenotype of myocardial hibernation (glycogen deposition and stable reduced regional contractile function).⁹⁶ In this way a decrease in the flow does not lead in a decrease in function and this is due to the switch in metabolic substrates and the accumulation of glycogen (increased metabolic reserve which permits some preservation of function). The down regulation of PPAR- α and PPAR- α regulated genes in this condition is partly controlled by reactive oxygen species (ROS).⁹⁷ It is postulated that the utilization of fatty acids in the post-ischemic myocardium leads to reactive oxygen species accumulation, which may be detrimental for the heart. The down-regulation of PPAR- α by ROS is therefore a protective mechanism which allows the preservation of metabolism and function. Another detrimental effect of a high concentration of fatty acids after reperfusion is the fact that they abolish the cardioprotective effect of insulin and its ability to inhibit AMPK.⁹⁸ This is probably related to the fact that AMPK activation is associated with acceleration of fatty acid oxidation in the reperfused heart⁹⁹ which leads to decreased glucose oxidation (Randle hypothesis).¹⁰⁰ At the same time, however, increased AMPK activation increases glycolysis.¹⁰¹ Its product, pyruvate, which cannot be oxidized leads to lactate and hydrogen ion accumulation. The result is acidosis which causes impairment of contractile function¹⁰², but also an inhibition of 5' nucleotidase.¹⁰³

Furthermore reactivation of PPAR- α in mice exposed to repetitive ischemia reperfusion worsened contractile function, induced micro-infarctions, and increased intramyocardial triglyceride deposition, features suggestive of cardiac lipotoxicity.⁹⁷ Similarly another study shows that the chronic activation of PPAR- α in the heart is detrimental to the recovery of cardiac power after ischemia and reperfusion.¹⁰⁴

In pigs with hibernating myocardium graded epinephrine infusion results in increased segment shortening and myocardial oxygen consumption in the absence of increase in blood flow.¹⁰⁵ The preserved function is associated with increased lactate uptake by the myocardium and no lactate production suggesting an adaptive mechanism that prevents supply-demand mismatch in this case. A classic example for cardio-metabolic reserve.

To summarize, the above data suggest that in hypoxia, preconditioning, and persistent stunning resulting in hibernating myocardium and in hibernating myocardium itself the relationship between contractile and metabolic reserve is preserved. What those conditions have in common is a switch to glucose as an energy substrate (acutely in hypoxia and preconditioning and long-term in hibernation) along with down-regulation of PPAR- α transcript levels reflecting decreased fatty acid oxidation.

Diabetes

The diabetic heart functions in an environment rich in FFAs and glucose.¹⁰⁶ Those two substrates compete with each other. The increased supply of FFA leads to increased intracellular levels of fatty acids. Fatty acid ligands activate the PPAR- α expression.¹⁰⁷ The PPAR- α then increases the expression of genes in three sites of the fatty acid utilization: a) transport in the cell,¹⁰⁸ b) import in the mitochondrion,³⁴ and c) fatty acid oxidation.¹⁰⁹ The PPAR- α overexpression in mouse hearts leads in increased fatty acid oxidation and repression of glucose uptake and utilization similar to the one noted in diabetic hearts.¹¹⁰ The glucose utilization is repressed in three levels: a) fatty acyl-CoAs inhibit insulin mediated glucose transport by inhibiting insulin receptor substrates¹¹¹ and protein kinase B,¹¹² b) fatty acyl-CoAs inhibit hexokinase, which phosphorylates glucose upon its entrance to the cell,¹¹³ and c) the increase in PPAR- α expression and activity leads to increased PDK4 expression and increased acetyl CoA/CoA ratio both of which inhibit the pyruvate dehydrogenase complex.¹¹⁴ Despite the decreased insulin-mediated glucose transport, the glucose uptake of the diabetic heart is comparable to the normal heart due to the hyperglycemia.¹¹⁵ Due to the inhibition of glucose utilization glycolytic intermediates accumulate in the cardiomyocyte.¹¹⁶ Initially all those changes which are accompanied by changes in the cardiomyocyte contractile proteins do not lead in major changes in contractile function.¹¹⁷ Thus, this is still a state of adaptation of metabolism to preserve function.¹⁰⁶

However, when diabetes progresses, or when additional stresses are posed on the heart, metabolic mal-adaptation occurs. The expression of PPAR- α decreases¹¹⁸ with concomitant reduction in fatty acid oxidation. Decreased expression of PPAR- α in obese Zucker diabetic fatty rats¹¹⁹ and PPAR- α regulated genes (MCAD, m-CPT I) in the obese Zucker rat heart¹²⁰ has been demonstrated. The mismatch between the increased fatty acid delivery and decreased oxidation leads to intramyocardial lipid accumulation. Indeed among patients with heart failure the higher levels of intramyocardial lipid deposition are noted in those with diabetes and obesity.¹²¹ Increased lipid accumulation in the heart can lead to insulin resistance as it has been shown for the skeletal muscle^{111,122} further impairing metabolism in the heart. Increased triglyceride deposition in the heart leads to elevated ceramide and inducible nitric oxide synthase levels both of which result in increased apoptosis of the cardiomyocyte and contractile dysfunction.¹¹⁹ Contractile dysfunction related to increased lipid accumulation in the cardiomyocyte has been demonstrated in several other studies of obesity and diabetes both in humans and animals.^{120,121} In addition to impairing contractile function elevated plasma free fatty acids can impair left ventricular diastolic function in severely obese patients.¹²³ Diastolic dysfunction may be related to the alteration of proteins of the sarcoendoplasmic reticulum like SERCA2 α . The down-regulation of myocyte enhancing factor 2C (MEF2C) and MEF2C-regulated genes (GLUT4, SERCA2 α , and MHC α) in the failing hearts of patients with diabetes suggests a transcriptional mechanism that might contribute to the pathogenesis and contractile dysfunction of heart failure patients with diabetes. Reversal of the diastolic dysfunction can be demonstrated after weight reduction in obese patients.

A second mismatch exists in the diabetic heart. This is between the maintained glucose uptake and the decreased glucose oxidation. Failure to control the glucose levels can lead to the development of insulin resistance.¹²⁴ Also the accumulated glycolytic products are shifted to the pentose phosphate and hexosamine biosynthetic pathways. Both result in activation of glucose sensing transcription factors like Sp1. As mentioned previously Sp1 can decrease the expression of MCAD which controls one of the rate limiting steps in fatty acid oxidation.⁶⁶ It has recently been shown that glucose decreases the expression of PPAR- α and PPAR- α regulated genes in islet cells.¹²⁵ Whether this is true for the heart as well is not yet known. This could though be another mechanism, which contributes to excessive lipid accumulation and contractile dysfunction in the diabetic heart, which functions in a

high fatty acid and glucose milieu. Glucose sensing transcription factors have also been implicated in the transcription of MHC isoforms and skeletal α -actin^{126,127} providing another link between metabolism and function.

As shown above insulin resistance and metabolic maladaptation can cause contractile dysfunction of the heart. Recently we have shown that by changing the metabolic profile, reducing myocardial lipid accumulation, and promoting the down-regulation of PPAR- α regulated genes, PPAR- γ activation leads to an increased capacity of the myocardium to oxidize glucose and to a tighter coupling of oxidative metabolism and contraction in the setting of insulin resistance and type 2 diabetes.¹²⁸ Similarly, Zhou, et al. showed that troglitazone (PPAR- γ agonist) lowered myocardial triglycerides and ceramide while completely reversing evidence of apoptosis and loss of cardiac function in obese rats.¹¹⁹

In summary, obesity and diabetes induce metabolic, histologic and functional changes in the heart. The first stage is that of adaptation where metabolism is altered so that cardiac function is maintained. In the second stage of maladaptation the metabolic mismatch leads to contractile dysfunction. Correction of metabolic dysregulation can reverse contractile dysfunction. However, the cardio-metabolic reserve is lost in the mal-adapted “lipotoxic” heart.

Heart Failure

The enzymes of fatty acid oxidation are reduced in the human failing heart.^{88,129} In addition to the reduction in fatty acid oxidation an increase in glucose oxidation has been demonstrated in the failing human heart.¹³⁰ Earlier studies performed in human heart by Bing and coworkers¹³¹ came to the conclusion that energy substrate metabolism was not altered in failing heart but that the heart was deficient to utilize energy for effective muscular contraction. The question whether metabolic changes are the cause or consequence of impaired contractile function in non-ischemic heart is still open today. The failing adult heart reverts to a fetal metabolic gene profile by downregulating adult gene transcripts.⁶⁸ Specifically, the levels of m CPT I, MHC α and GLUT 4 decrease while MHC β increases⁶⁷. Those changes were similar to the ones induced by hypertrophy. It was proposed that similar changes during both hypertrophy and unloading may reflect an adaptation to the heart in the energy requirements while preserving function. Indeed those changes in the unloaded heart may contribute to the improvement in left ventricular function of some patients after the implantation of left ventricular assist devices.

Loss of this adaptation may lead to advanced stages of heart failure. In a recent study down-regulation of PPAR- α , mCPT1 and MCAD was noted in the failing compared to the non-failing hearts.¹²¹ In failing hearts though with significant lipid accumulation upregulation of PPAR- α regulated genes was noted (MCAD, mCPT1) similar to the lipotoxic ZDF rat heart. We proposed that when the failing heart (which adapts with down-regulation of the FAO pathways) faces an increased fatty acid load (as in diabetes or obesity), intramyocardial lipid accumulation occurs. This is associated with an up-regulation in PPAR α activity and in MHC- β transcript levels.¹²¹ Both lead in further contractile dysfunction. Similarly, reactivation of PPAR α was shown to have detrimental effects during a) repetitive ischemia and reperfusion leading to cardiac lipotoxicity,⁹⁷ b) in recovery of cardiac power after ischemia and reperfusion,¹⁰⁴ and c) in a pressure-overload model of hypertrophied rat heart.⁸⁶

Lastly, in a model of experimental mitral regurgitation (MR) it was shown that chronic MR leads to intramyocyte myocardial lipid accumulation and contractile dysfunction. As in the cases of diabetes and obesity mentioned before, the administration of the PPAR- γ agonist rosiglitazone ameliorated MR-induced LV dysfunction accompanied by a decline in lipid

content.¹³² This occurs most likely by restoring the faulty energy substrate utilization, another proof of the tight link among metabolism and function.

Conclusion

The heart responds to inotropic stimuli by increasing its contractile function, which is accompanied by an increase of coronary flow. This response can only be accomplished by an appropriate metabolic response. The match between contractile and metabolic reserve is characteristic of metabolic adaptation. Breach of this balance results in maladaptation with detrimental consequences for myocardial function.

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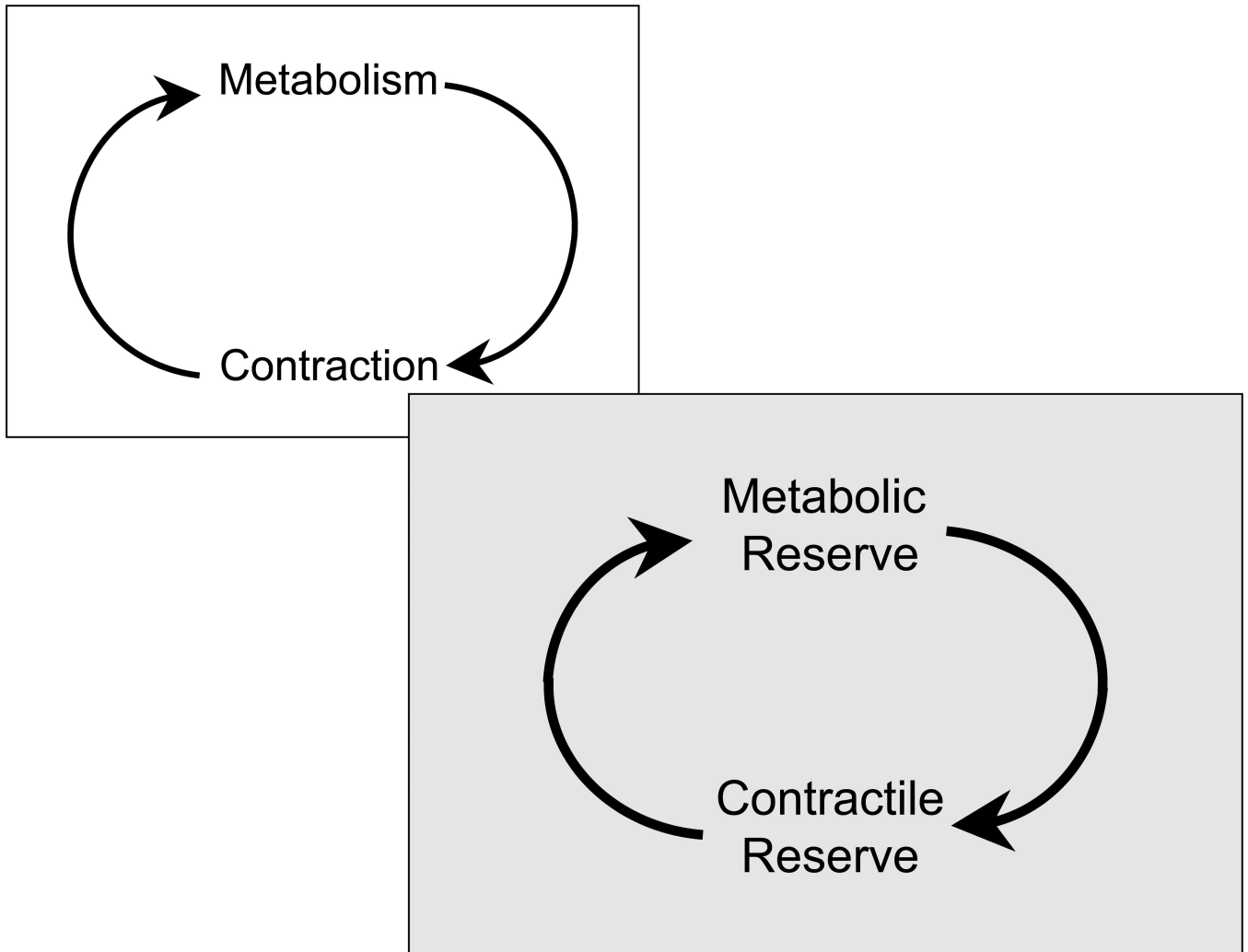


Figure 1. A single schematic showing the tight link between metabolism and contractile function of the heart. Increased contractile performance requires increased rates of energy substrate metabolism. See text for further discussion.

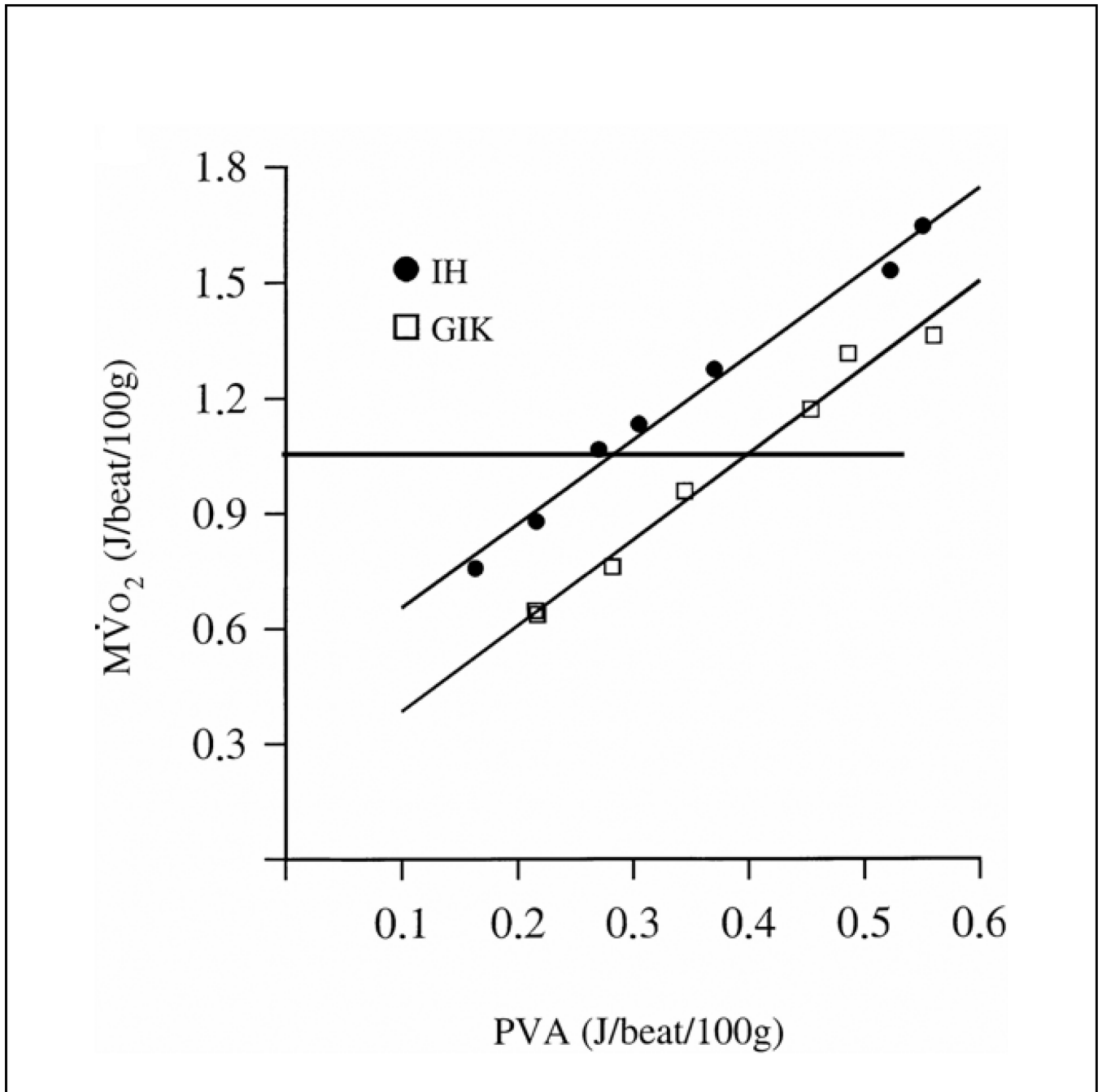


Figure 2. Relationships between $\dot{M}V\text{O}_2$ and PVA from one representative experiment. Modified with permission from Korvald et.al.¹⁹

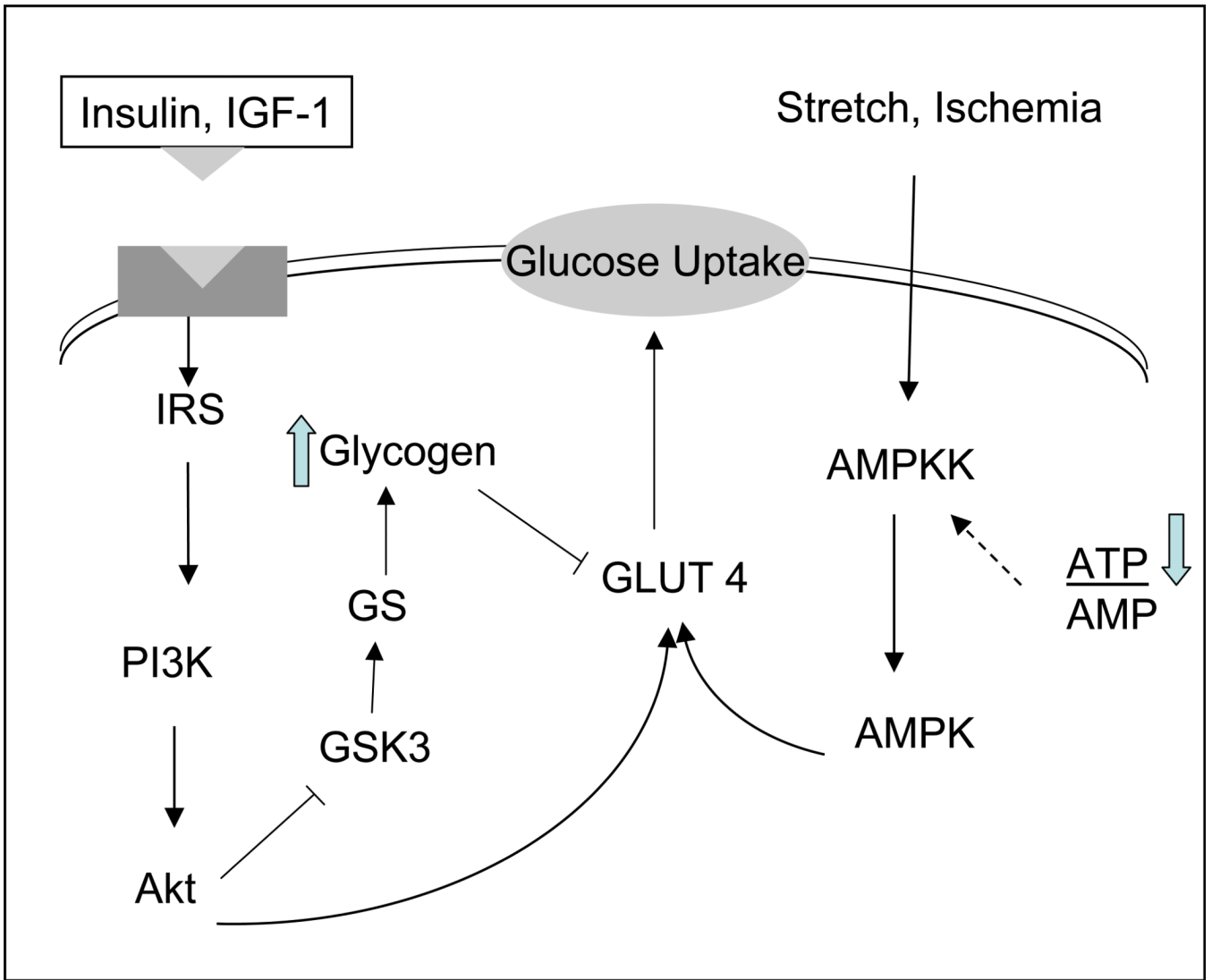


Figure 3. Receptor dependent and receptor independent translocation of GLUT4. See text for further discussion.

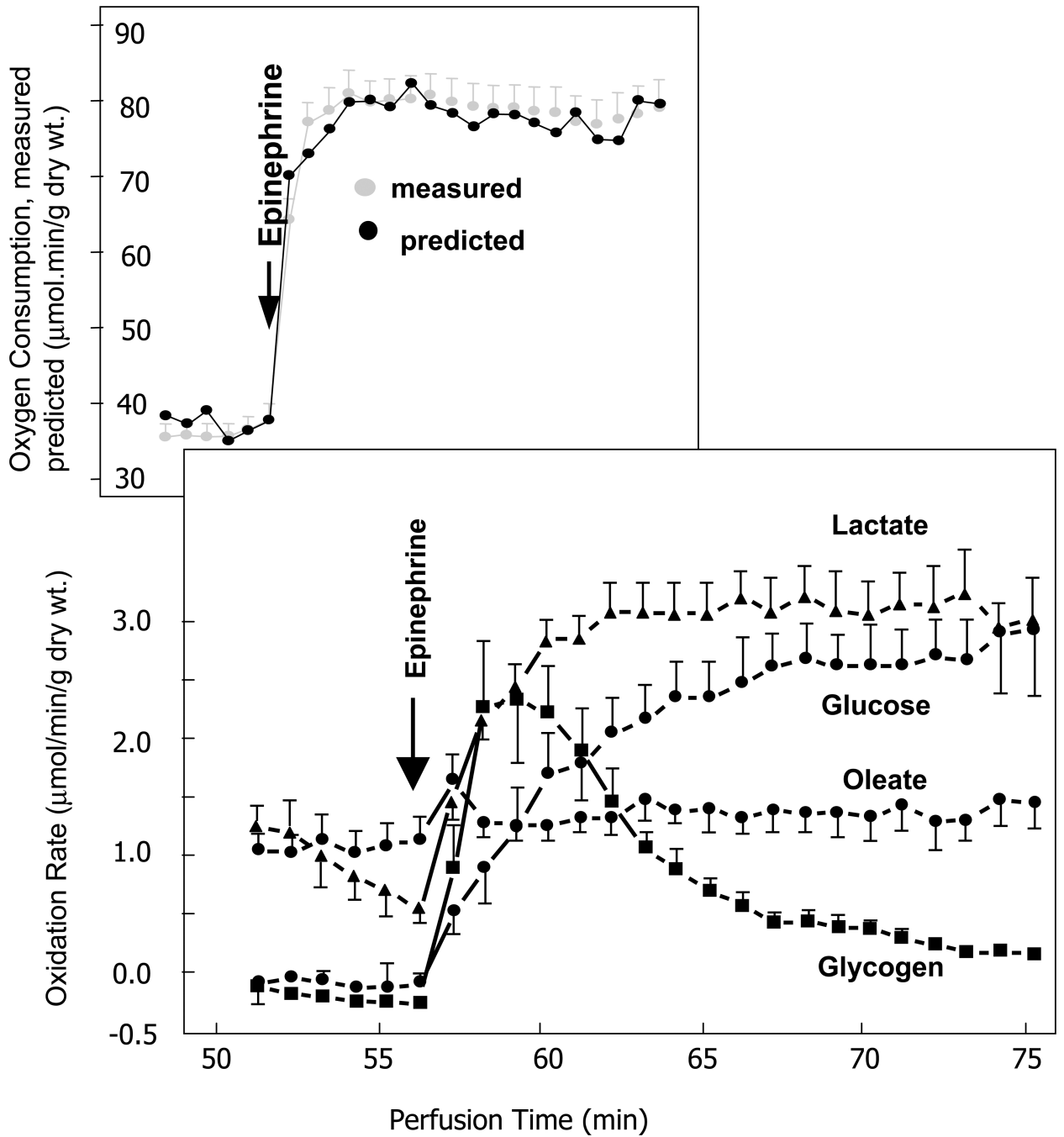


Figure 4.

Rates of substrate oxidation. Rates during the chase period of the protocol are depicted. ●, $^{14}\text{CO}_2$ from exogenous [U- ^{14}C]glucose; ■ $^{14}\text{CO}_2$ from [^{14}C]glycogen; ▲, $^{14}\text{CO}_2$ from exogenous [U- ^{14}C]lactate; ○, $^3\text{H}_2\text{O}$ from exogenous [9,10- ^3H]oleate. Values for glycogen were corrected for incomplete labeling assuming uniform isotopic dilution at an enrichment of 54.7%. Values are the mean \pm 6 S.E. for five perfusions in each treatment group. Adapted from reference 47. See text for further details.

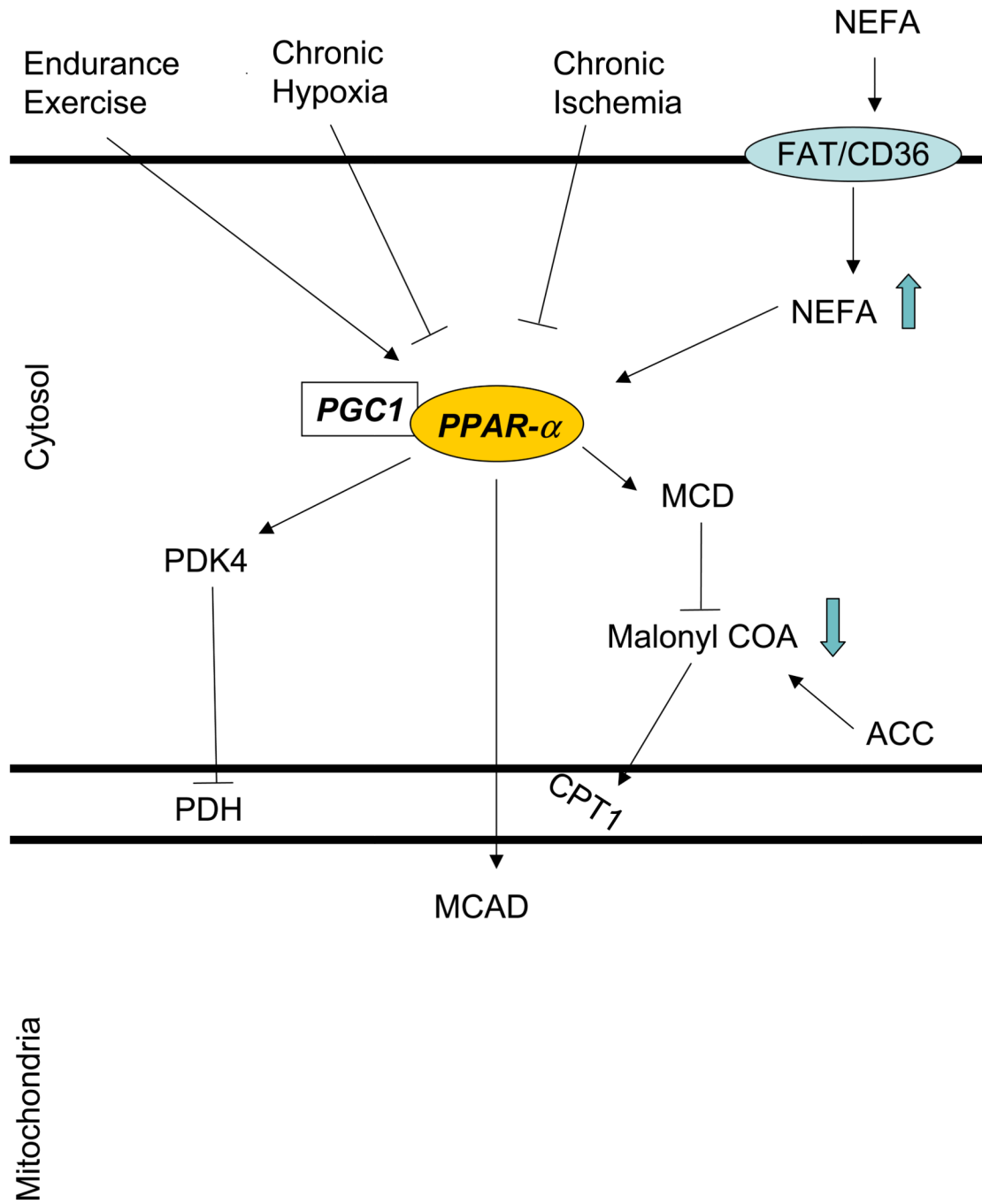


Figure 5. Fatty acid metabolism is regulated at the transcriptional level. See text for further details.

Table 1

Energy Stores in the Muscle

Compound	Rate of Mobilization/ Rate of Restoration	Energy yield (Kj/g wet weight)
Phosphocreatine	Very fast	0.204
Glycogen	Fast	16
Triglycerides	Slow	35