Myocardial Substrate Metabolism in Obesity

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Abstract

Obesity is linked to a wide variety of cardiac changes, from subclinical diastolic dysfunction to end stage systolic heart failure. Obesity causes changes in cardiac metabolism that make ATP production and utilization less efficient producing functional consequences that are linked to the increased rate of heart failure in this population. As a result of the increases in circulating fatty acids and insulin resistance that accompanies excess fat storage, several of the proteins and genes that are responsible for fatty acid uptake and metabolism are up-regulated, and the metabolic machinery responsible for glucose utilization and oxidation are inhibited. The resultant increase in fatty acid metabolism, and the inherent alterations in the proteins of the electron transport chain used to create the gradient needed to drive mitochondrial ATP production, results in a decrease in efficiency of cardiac work and a relative increase in oxygen usage. These changes in cardiac mitochondrial metabolism are potential therapeutic targets for the treatment and prevention of obesity related heart failure.

Introduction

Cardiac energy metabolism is essentially a four step processes involving 1) myocellular substrate uptake/selection, 2) mitochondrial ATP production, 3) ATP transfer from site of production (mitochondrion) to 4) the site of ATP utilization (cardiac myofibril, Figure 1) (1).

Although glycolysis is an ATP generator, overall ATP production is controlled largely by the rate at which the Krebs (Tricarboxylic Acid, TCA) cycle operates. (2) Acetyl CoA, which is produced from the oxidation of fatty acids, ketone bodies, or glucose via glycolysis and the pyruvate dehydrogenase (PDH) enzyme complex (3) enters the Krebs cycle for complete oxidation. During oxidative phosphorylation electrons, primarily obtained from oxidative metabolism of carbohydrates and fats, are transferred through the electron transport chain, a 4 complex protein system embedded within the inner membrane of the mitochondria. The major function of the electron transport chain is to produce a proton electrochemical potential difference between two compartments that powers ATP synthase to generate ATP, which is used for all cardiac cellular processes.(4)

ATP is the heart's only immediate source of energy for contraction and as both systole and diastole are adenosine tri-phosphate ATP consuming processes, (5, 6) cardiac ATP demand is very high. In order to keep up with this demand for continuous and efficient contraction and relaxation, the heart needs to produce around 20 times its own weight in ATP per day.(1) As a result of this large energy requirement, any impairment in ATP production, transfer or utilization can have detrimental effects on cardiac function. (7) Cardiac metabolism and ATP production is altered in obesity and has emerged as candidate mechanism to explain the increase in heart failure in this population. (8) Indeed, it has recently been shown that obesity, in the absence of co-morbidities, is linked to impaired myocardial high energy phosphate metabolism (9) and diastolic dysfunction, (10-12) both markers of increased cardiovascular

risk,(13) providing a mechanistic link between altered myocardial energy production and mortality.

However, although it is well recognized that a subset of obese subjects are free of the associated metabolic co-morbidities, it is well known that the majority of obese subjects are at risk of insulin resistance, diabetes and hypertension, all of which are known to independently effect cardiac energy metabolism. (5, 14) As such isolating the effects of obesity, per se on cardiac metabolism is difficult, but given the ever increasing incidence of obesity and its links to heart failure (8) and mortality (15), understanding the alterations of myocardial metabolism that occur in obesity are of great importance and may provide therapeutic options to treat or prevent cardiac dysfunction. This review focuses on the current knowledge of the changes in myocardial metabolism that occur in obesity without established co-morbidities.

Methods

Relevant articles were selected from Pubmed. Initial search term was "Myocardial, Metabolism, Obesity" which revealed 1877 articles. This was refined to "Myocardial Energetics Obesity" (11 articles), myocardial substrate selection (80 articles) myocardial substrate metabolism obesity (64 articles), myocardial substrate metabolism weight loss (24 articles) and partial fatty acid oxidation inhibitors heart (23 articles). Of these 202 articles, 88 were excluded for not having a direct relevance to obesity and 114 were finally selected for the review.

Altered Myocardial Substrate Selection in Obesity

Myocardial substrate selection is a fundamental step in myocardial metabolism. In the normal heart in the resting, fasted state, the vast majority (60-90%) (16) of the acetyl CoA that enters the Krebs cycle comes from the β-oxidation of free fatty acids (17) with 10–40% of acetyl CoA coming from the oxidation of pyruvate, which itself is derived from either glycolysis or lactate oxidation. (Figure 2) (18) However, the heart is able to display great flexibility in its choice of substrate depending on the prevailing metabolic conditions.(19) For example, in the uncontrolled diabetic state, because of the combined effects of insulin resistance and high circulating free fatty acids, the myocardium uses fatty acids almost exclusively to support ATP synthesis.(20)

This remarkable ability of the heart to switch between metabolic substrates appears to be a part of natural foetal development where a switch in cardiac fuel preference from glucose to fatty acids occurs just after birth, when oxygen availability and dietary fat content abruptly increase, making fatty acid oxidation more preferable than glucose oxidation. The importance of this neonatal metabolic switch to fatty acid preference is apparent in children with mutations in medium chain acyl-CoA dehydrogenase (MCAD) and very long chain acyl-CoA dehydrogenase (VLCAD), genes involved in fatty acid β-oxidation, who develop a cardiomyopathy during periods of illness or metabolic stress. (21) The importance is again highlighted in the setting of heart failure and left ventricular hypertrophy, where mitochondrial oxidative capacity is reduced, metabolism shifts back towards a reliance on glucose metabolism, resembling the foetal metabolic program. (22, 23)

As the heart is an extremely efficient scavenger of circulating non-esterified free fatty acids (up to 40% extraction fraction), (24) the rate of fatty acid uptake by the heart is primarily determined by the concentration of non-esterified fatty acids in the plasma.(25) The concentration of serum free fatty acids is highly regulated and represents a balance between production via hormone sensitive lipase induced adipose tissue triglyceride breakdown and

synthesis via glycerolphosphate acyltransferase.(25) As hormone sensitive lipase is activated by catecholamines and inhibited by insulin, this allows the plasma free fatty acid concentration to rise during periods where glucose supply is limited (e.g. exercise or fasting), resulting in a higher rate of cardiomyocyte uptake and utilization. (25, 26)

Fatty acid movement into the cardiomyocyte occurs either by passive diffusion or by protein-mediated transport across the sarcolemma via fatty acid translocase (FAT/CD36), or fatty acid binding protein (FABP). (27) Once inside the cell, control of fatty acid oxidation occurs at the level of mitochondrial uptake of fatty acids by carnitine palmitoyltransferase 1 (CPT1). CPT1 is associated with the outer mitochondrial membrane and mediates the transport of long-chain fatty acids across the membrane by binding the fatty acid moiety from acyl–coenzyme A (CoA) to long chain acylcarnitine, which is then transported into the mitochondria. (28, 29) CPT1 is inhibited by malonyl-CoA, an important regulator of fatty acid oxidation in the heart. Malonyl-CoA, the first intermediate in fatty acid synthesis, is produced by acetyl-coA carboxylase (ACC) and is broken down by malonyl-CoA decarboxylase.(30) AMP-activated protein kinase (AMPK) regulates malonyl-CoA levels by phosphorylating and inhibiting ACC, increasing fatty acid oxidation (Figure 2). (31) Obesity is linked to increased circulating free fatty acid levels (32) and both human (33) and animal studies (34, 35) have shown increased oxidation of free fatty acids in obesity and insulin resistance, and a shift in substrate utilization further towards free fatty acid metabolism (Figure 3).

The crucial importance of this increase in fatty acid metabolism lies in the fact that mitochondrial redox state, and as a result the free energy of hydrolysis of ATP, is affected by the substrate oxidised. In order to understand this effect we have to consider the relationship between the thermodynamic relationship between ΔG (Gibbs free energy, a thermodynamic potential that measures the process initiating work obtainable from a thermodynamic system)

and ΔH (change in enthalpy or heat energy). Fundamentally our body is driven by a series of controlled chemical reactions, resulting in the oxidation of carbon substrates to water and CO_2. Thus for a given amount of substance, the maximum amount of non-expansive work that can be obtained from a closed system is denoted by the Gibbs free energy. Described in 1873 (36), this application of the second law of thermodynamics can be readily translated to biological systems, and in its simplest form relates enthalpy and entropy to a conservation of energy. Put formally as:

$$\Delta G = \Delta H - T\Delta S$$

This equation, in part, explains why certain substrates (with higher enthalpy) yield greater potential energy to power a system, the larger the value of Gibbs free energy the more energy that can be exchanged with the surrounding system. In non-standard chemical conditions such as are present in most biological systems(37), an alternative form of this equation is used.

$$\Delta G' = \Delta G° + RT\,ln\,Q$$

This equation allows the integration of the reaction quotient (Q) into the relationship between free energy and the chemical conditions under which the reaction is taking place. In the case of cellular substrate energetics, the final common endpoint for the complete oxidation of carbon fuels is the conservation of energy in the phosphate bonds of ATP. Therefore applying this concept to the equation above, the inherent energy stored in this bond ($\Delta G_{\text{ATP hydrolysis}}$) can be calculated from the equation (38-47)

$$\Delta G' = \Delta G° + RT\,ln\,\frac{[ADP][Pi]}{[ATP]}$$

Despite the apparent simplicity of oxidising substrates to liberate energy to perform work, the useful free energy of substrate combustion is influenced by the architecture of the metabolic pathway and the enthalpy of that particular substrate. For this reason the available free energy to perform work, the free energy of ATP hydrolysis ($\Delta G'_{\text{ATP hydrolysis}}$) is not equivalent for all dietary fuels. Since the conversion of ADP + Pi to ATP is driven by the electrochemical potential difference across the mitochondrial membranes, the equation for free energy can now be expressed as:

$$\Delta G' = -n\ F\ \Delta E_{\text{inter/matrix}}$$

(where $\Delta G'$ is the free energy, *n* the number of electrons, *F* the Faraday constant, and ΔE the difference in redox potential between'Inter' and 'Matrix' denoting the separate mitochondrial phases partitioned by the inner mitochondrial membrane (48),(46). It then becomes apparent that the larger the electrical potential difference between mitochondrial phases created by the pumping of protons into the intermitochondrial space (49), the greater the potential free energy. An increase in redox energy of the respiratory chain, results in an increase in the energy of the protons expelled from the mitochondria at the energy conserving sites, which is then reflected in an increase in the energy of ATP hydrolysis.We can express the potential energy of this proton gradient as:

$$\Delta G'\ [H^+]_{Inter}/[H^+]_{Matrix} = RT\ \ell n\ [H^+]_{Inter}/[H^+]_{Matrix} + FE_{\ Matrix/Inter}$$

Therefore the relative supply of reducing equivalents generated by the architecture of each pathway also has a significant influence on mitochondrial potential gradients, and thus the $\Delta G'_{\text{ATP hydrolysis}}$(50, 51) (43).

Hence, whilst the electron transport chain is in itself a remarkably efficient series of biochemical reactions (52), the free energy of ATP hydrolysis is not identical for all

substrates. (53) (50, 51)(Figure 4). Heat of combustion is also of inherent importance when considering the potential impact of mitochondrial substrate selection on energetic performance. Pyruvate, the end product of glycolysis, has a lower heat of combustion per C_2 unit than palmitate, providing less potential energy to the electron transport chain.

However, fatty acid metabolism, despite its large potential energy, is not able to provide greater mitochondrial redox power. The reasons for this lies in the architecture of fatty acid metabolism by β-oxidation, and the changes in mitochondrial membrane uncoupling proteins in response to persistently elevated FFA. Only 50% of the reducing equivalents produced in the process of β-oxidation are able to donate electrons at complex I of the electron transport chain, whereas the remaining half are donated by $FADH_2$ at the flavoprotein site further 'downstream' at complex II (48). This results in a reduced ATP yield and a loss of mitochondrial efficiency. The redox span of the respiratory chain is diminished during fat metabolism as the Q couple is reduced. This decreases the potential difference between matrix and inter-mitochondrial membrane space and therefore $\Delta G'_{ATP}$. Raised free fatty acids also increase the expression of uncoupling proteins (54), which decrease mitochondrial efficiency (43) by allowing the passage of protons into the matrix via non ATP generating pathways. Indeed, when the heart is perfused with increasing concentrations of free fatty acids, this results in an additional oxygen cost of between 25% and 48% for the same work output when compared to glucose and insulin infusion (55). The loss of myocardial efficiency when metabolising fat has been attributed to reductions in mitochondrial electron transport chain coupling, and the increased stoichiometric oxygen requirement to oxidise fat (56). As such, deleterious substrate selection may be a feature of obesity related cardiomyopathy as it is in other myocardial diseases, intimately linking energetic performance and mortality (56, 57).

In addition, Positron Emission Topography (PET) studies have shown that in human obesity myocardial fatty acid uptake is increased and myocardial efficiency reduced, (if calculated as cardiac work / oxygen usage).(58) This is in keeping with the increased utilization of fatty acids for ATP production, and suggests either a decoupling of fatty acid oxidation and ATP production or futile cycling of substrates in the obese heart with energy wastage.(59) Elevations in free fatty acid levels are thought to increase mitochondrial uncoupling, and energy wastage, via increased myocardial uncoupling protein 3 (UCP3) expression. (60) (61)As diastole is more susceptible to ATP shortage than systole, this would then lead to a mechanism by which reduced high energy phosphate levels, caused by increased mitochondrial uncoupling as a result of elevated free fatty acid levels, may manifest as diastolic dysfunction, an almost universal finding in obesity.(10, 11)

This shift towards fatty acid metabolism appears to be a combination of reduced insulin-induced GLUT4-mediated glucose uptake (62) (63), suppressed glycolysis in the cytosol and reduced pyruvate dehydrogenase flux in the mitochondria, reducing carbohydrate oxidation. Although the complexities of the inhibition of cardohydrate metabolism are not fully elucidated, the inhibition of glucose oxidation by fatty acids at the level of the pyruvate dehydrogenase (PDH) complex is universally reported, and has been termed the glucose-fatty acid or Randle cycle. (64-66)Up until very recently the vast majority of experimental data for altered substrate selection in obesity and insulin resistance were from *ex vivo* and *in vitro* studies. These studies are however limited, in that most generate steady-state, rather than real-time, information. The development of hyperpolarized ^{13}C MR, in which the ^{13}C signal is amplified by >10,000-fold, provides a solution to this and has allowed real-time visualization of substrate uptake and metabolism. So far, these studies have been focused primarily on PDH activity, which, given its pivotal position in the glucose–fatty acid cycle, has allowed further insight into cardiac substrate selection (67) and have again shown

that *in vivo* real time PDH activity is decreased in diabetic (68) and high fat diet animal models. (69)

Furthermore, in addition to the effects of increased fatty acid uptake and utilization on the production of the electrochemical gradient that powers ATP production, there is now evidence that there are intrinsic defects in the metabolic machinery of the electron transport chain (complexes I,III and IV) in human and animal models of obesity with electron transport chain function and efficiency being reduced.(70-72) (35, 71, 73)

As a result of the evidence that substrate selection alters myocardial efficiency several novel therapies have been evaluated in setting of ischaemia, a situation where reducing myocardial oxygen consumption (MVO_2) without decreasing cardiac work would be beneficial. In these settings a shift in the proportions of ATP generated from fatty acid oxidation towards glucose oxidation would provide the heart with an efficient method to maintain a constant fuel source in the face of hypoxia. To date several partial fatty acid oxidation inhibitors acting either via CPT-1 (Perhexiline) (74) or via directly inhibiting fatty acid oxidation (Trimetazidine) have been shown to be beneficial in heart failure, ischemic heart disease and animal models of pulmonary hypertension. (75, 76) However, therapies aimed at altering substrate metabolism in obesity have been limited to ischaemia reperfusion models, (77) and further investigation of the effects of fatty acid oxidation inhibitors are warranted in obesity.

Cardiac Energetics and Obesity

Heart failure, a well documented sequelae of obesity (8), is associated with deranged cardiac energetics, (1) i.e. a decreased efficiency of substrate utilization to create the ATP necessary to drive cardiac contraction. This has also been demonstrated in other cardiovascular disorders such a hypertensive heart disease and diabetes [24, 25]. Using ^{31}P-MRS, cardiac energetics can be assessed by quantifying the relative concentrations of

phosphocreatine (PCr) and adenosine triphosphate (ATP) in the myocardium to derive the PCr/ATP ratio, a sensitive index of the energetic state of the heart. In heart failure, the PCr/ATP ratio correlates with LV function[26] and clinical status[27], and has been shown to be a better prognostic indicator than LV ejection fraction[28]. Improving cardiac metabolism has been postulated as a novel treatment of heart failure.[23, 29] It has been shown that animal models of obesity (35) and in humans with no other co-morbidity, that abnormally low PCr/ATP ratios occur at rest, potentially due to, in addition to changes in substrate utilization, a loss of the total creatine pool, in proportion to the loss of PCr, as occurs in many other forms of hypertrophy. (1, 78, 79). (80) (81) Furthermore this has been linked to altered cardiac diastolic function and is exacerbated during catecholamine stress. (80)

Mitochondrial Metabolism and Lipotoxicity in Obesity

Cardiac mitochondria contain a DNA genome that encodes some of the proteins required for electron transport complexes I, III, IV, and in addition, complex V. The remainder of the respiratory subunits, and all of the proteins required for substrate metabolism are encoded by separate nuclear genes.(82) It is becoming clear that in obesity, changes in both nuclear and mitochondrial transcription are present and are important in the production of the observed changes in cardiac metabolism. (61)

One of the key controllers of nuclear gene transcription which regulates myocardial mitochondrial fatty acid oxidation are the peroxisome proliferator-activated receptors (PPARs) (83) which, when activated, induce perixosome proliferation. Peroxisomes have multiple metabolic roles which include long and very long chain fatty acid oxidation. (84) Three PPAR receptors have been identified: PPAR γ, PPAR δ, and PPAR α, all with different tissue expression. PPAR α is expressed in the myocardium, (85) and is the primary transcriptional regulator of fat metabolism in tissues with the highest rates of fatty acid

oxidation. (86) Activation of PPARα in the heart increases the expression of several genes involved in fatty acid metabolism including; a) cardiac myocellular fatty acid uptake (FATP, FAT/CD36, FABP, ACS (87-89) b) mitochondrial fatty acid uptake via CPT I (90) and c) mitochondrial and peroxisomal fatty acid β-oxidation via MCAD, LCAD, VLCAD and ACO respectively (Figure 3). (90)

In the setting of insulin resistance, like obesity, the heart initially adapts to increases in circulating fatty acid levels by increasing PPARα, resulting in a compensatory increase in myocardial fatty acid uptake and β -oxidation, (91) which is believed to limit cardiac ectopic lipid accumulation. A further protective mechanism against ectopic cardiac fat deposition has been suggested in obese animal models with increased cardiac expression of microsomal triglyceride transfer protein, and increased formation of apolipoprotein B-containing lipoproteins which are then secreted by cardiomyocytes. (92)

However, despite these initial adaptive/protective mechanisms, the potential for cardiac lipotoxicity in obesity has been described. (93) Fatty acid inhibition of myocardial glucose use appears to be one important contributing factor. (94, 95) Exposure of the heart to high levels of fatty acids can cause accumulation of lipids within cardiomyocytes increasing the intracellular pool of long-chain fatty acyl-CoA which provides a fatty acid substrate for nonoxidative processes, including triacylglycerol, diacylglycerol, and ceramide synthesis, which can lead to cell dysfunction, insulin resistance, and potentially apoptotic cell death. A clear link between lipid accumulation and cardiomyopathy has now been established in several transgenic mouse models in which the rate of lipid uptake or esterification of fatty acids by the heart was increased or the capacity for oxidation of fatty acids was reduced in the mitochondria. (93) (96)

In addition to the PPARα mediated increases in fatty acid oxidation, cardiac myocytes from Zucker obese rats have a larger proportion of FAT/CD36 (97, 98) located at the plasma membrane when compared with Zucker lean rats. (99) Normal insulin mediated translocation of FAT/CD36 is not seen in Zucker obese rats, supporting the notion that a substantial portion of the FAT/CD36 pool is permanently relocated to the sarcolemma in the heart in obesity and that this enables triglyceride accumulation via increased fatty acid uptake. (100) GLUT4 expression is also altered by excessive nutrient intake. In normal cardiac tissue insulin causes the mobilization of GLUT4 from intracellular stores to the sarcolemma. However, in obesity, and insulin resistance this process is reduced. Put together with the evidence of altered FAT/CD36 positioning, this suggests that excessive nutritional intake causes a pattern of distribution of FAT/CD36 and GLUT4 that is directed towards increased fatty acid uptake and ectopic fat deposition. (100)

Although there is good evidence that lipid accumulation can cause cardiac dysfunction, whether or not the accumulation of triglyceride in the heart is a purely maladaptive process contributing to cardiac dysfunction has recently come under scrutiny. There is now alternative evidence to suggest that cardiac triglyceride accumulation may be providing a protective role against fatty acid induced lipotoxicity via limiting the accumulation of ceramides and diacylglycerols. (101) However, regardless of whether ectopic lipid deposition is a maladaptive or a protective process there is now strong evidence that myocardial steatosis promotes the development of insulin resistance, cardiac hypertrophy, impaired cardiac function and fatty acid induced programmed cell death, and interstitial fibrosis. (102)

Adipokine Regulation of Myocardial Metabolism

It is now well established that adipose tissue secretes a range of adipokines (eg, leptin, adiponectin, resistin, ghrelin, visfatin) that alter fat metabolism. (103) Obesity affects the levels of these hormones, and two of these, namely leptin and adiponectin, have been shown to modulate myocardial substrate metabolism. Adiponectin is believed to act via PPARα to stimulate fatty acid metabolism, increase CPT1 activity and decrease malonyl-CoA inhibition of CPT1 activity. (104, 105) However, as adiponectin is significantly lowered by obesity, (106) and fatty acid metabolism is increased, the full role of adiponectin in myocardial metabolism in obesity remains unknown. In contrast, leptin increases with increasing obesity (107) and has been shown to increase myocardial fatty acid metabolism and decrease myocardial glucose metabolism, in line with the observed changes seen in obesity. This increase in fatty acid oxidation occurs independent of changes in insulin signaling and PPARα transcriptional regulation but may be attributable to increased fatty acid transport proteins on the plasma membrane. (108) It has also been postulated that leptin plays an important role in the prevention of cardiac lipotoxicity by confining the storage of excess lipids to adipocytes, while simultaneously limiting the storage of intracellular lipids in myocytes and other nonadipocytes. (109)

The Effects of Weight Loss on Myocardial Metabolism

As obesity is associated increased myocardial fatty acid uptake and oxidation, lipotoxicity and decreased myocardial energetics, all known to be detrimental to cardiac function, understanding the effects of weight loss are of increasing importance. Weight loss interventions have not only been shown to decrease myocardial free fatty acid uptake without changing insulin-stimulated myocardial glucose uptake, (110) but also to reduce myocardial fatty acid oxidation (per gram of left ventricle), and that this decreased fatty acid oxidation is linked to decreased MVO_2 (myocardial oxygen uptake per gram of left ventricle). (111) Put together this strengthens the evidence that increased fatty acid uptake and oxidation in

obesity is linked to decreased cardiac efficiency, and that weight loss partially reverses these effects. In addition to this, moderate dietary weight loss has been shown to significantly reduce myocardial triglyceride content (112) and improve both myocardial energetics and diastolic function in obese subjects without cardiovascular risk factors.(113) Weight loss surgery has also been shown to provide early adjustments of the metabolic and neurohumoral pathways involved in energy homeostasis and reverse obesity-related hemodynamic, metabolic, and cardiac dysfunction.(114) Given this clear benefit of the reduction in fatty acid oxidation rates that accompany weight loss, further understanding of cardiac metabolism in obesity may lead to therapeutic options to modulate metabolism and treat cardiac dysfunction in obesity.

Conclusion

Obesity is an escalating problem and is linked to a spectrum of cardiac dysfunction from subclinical changes in diastolic function to severe systolic heart failure. There is now emerging evidence that alterations in myocardial substrate selection in obesity towards increased fatty acid oxidation and away from glucose metabolism, results in decreased contractile efficiency and may well underpin the susceptibility to contractile dysfunction in this population. The heart in obesity is also characterized by an accumulation of intracellular triglycerides and lipids that promote lipotoxicity and dysfunction. As novel imaging techniques are now providing a greater detail of this altered myocardial metabolism in vivo, potential targets for therapeutic interventions aimed at preventing and treating the cardiomyopathy of obesity via altering myocardial metabolism are likely to become a reality.

Conflicts of Interest: None

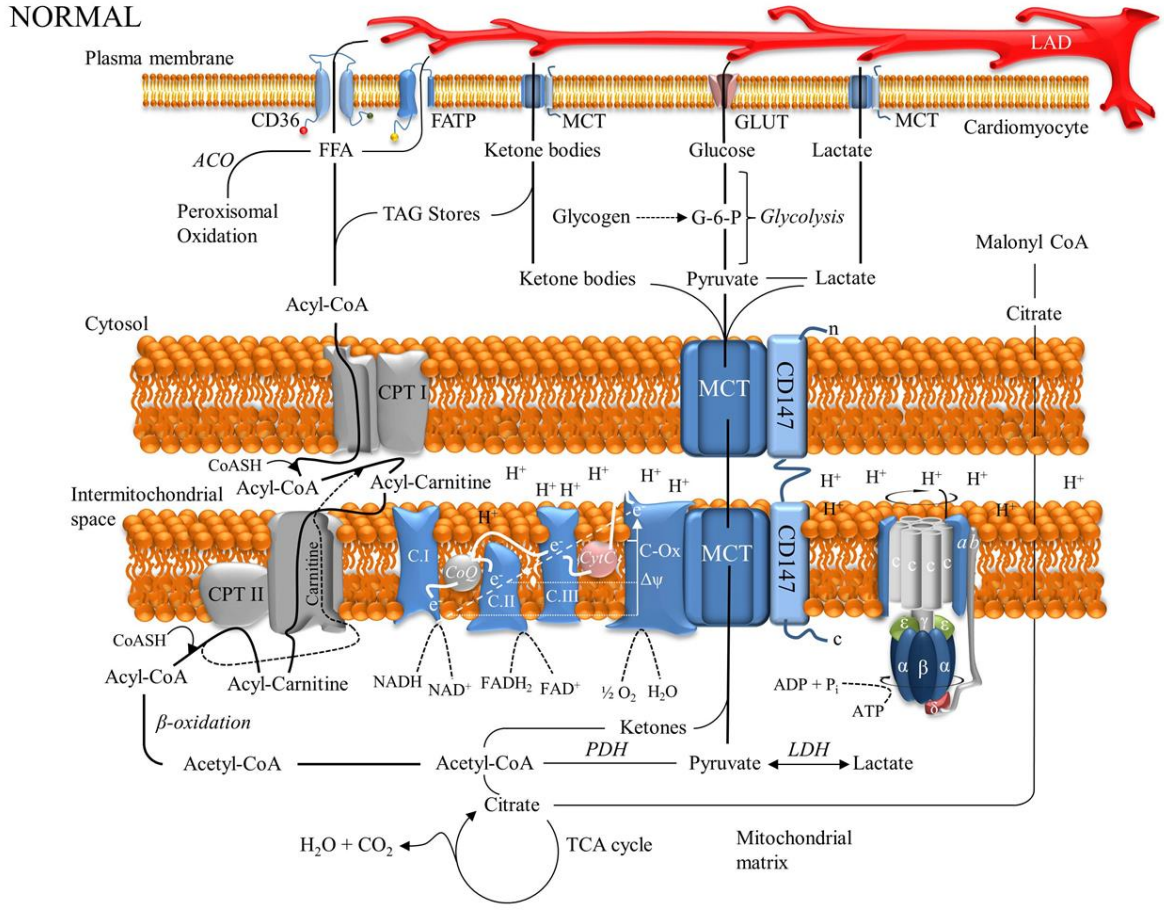

Figure 2. Normal Myocardial Metabolism.

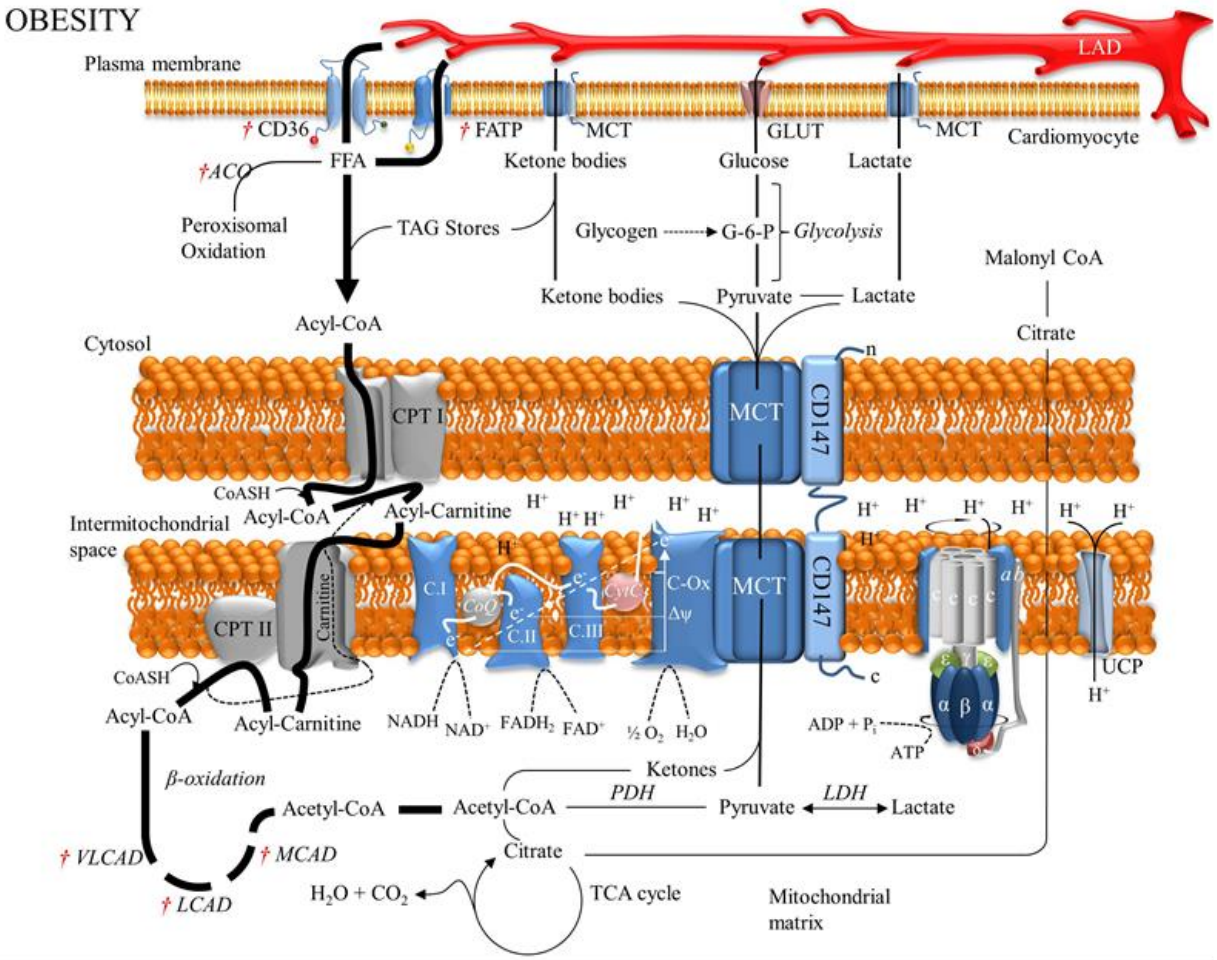

Figure 3. Changes in Myocardial Metabolism in Obesity (red cross denotes PPARα mediated change).

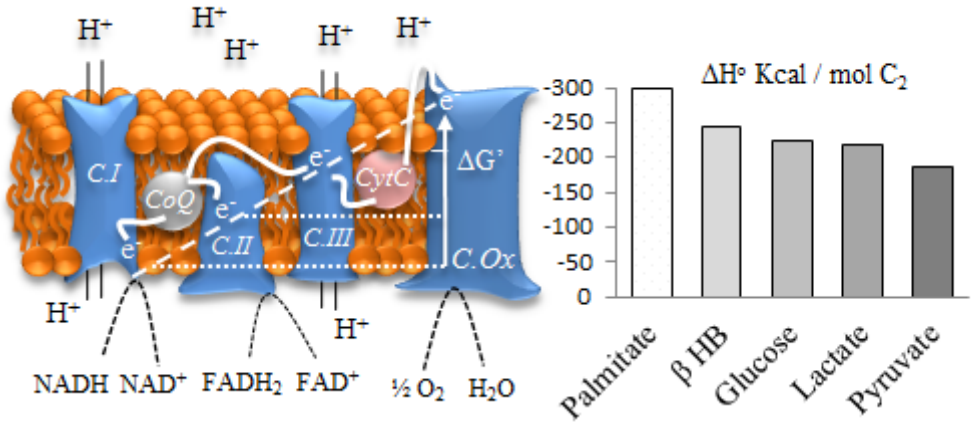

Figure 4. The effect of varying substrate selection on the ΔG produced by the Electron Transport Chain.

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