Overview

Axel Gödecke

Anatomy and Physiology of the Heart

The circulatory system, consisting of the heart and arterial, venous, and capillary blood vessels, delivers oxygen and nutrients to all organs and transports metabolites to sites of further metabolization and excretion. To execute this central role, the heart continuously pumps the blood through the vasculature (see chapter "Overview" under part "Blood vessels"). Although the heart is a single organ, in terms of function, it represents two pumps working in series. Whereas the left heart generates high pressure (basal level 120 mmHg) to supply all organs (except the lung) with oxygenated blood, the right heart enables blood flow through the pulmonary vasculature by generating a low-pressure gradient (basal level 20 mmHg). Left and right hearts show a similar gross anatomy: both consist of an atrium and a ventricle, which are separated by a septum. Due to the differences in workload, the muscle mass of the left ventricle exceeds that of the right one. To achieve a directed blood flow, inlet valves (i.e., mitral and tricuspid valves) separate the atria from the ventricles, and outlet valves (aortic and pulmonary valves) separate the ventricles from the aorta and pulmonary artery (Fig. 1).

The cardiac cycle is subdivided into two major parts: During systole, the walls of the blood-filled ventricles rapidly contract, resulting in a steep rise of left ventricular pressure. Since the aortic and mitral valves of the left ventricle are closed at the beginning of systole, the first phase represents an isovolumic contraction. However, when left ventricular pressure exceeds that in the aortic root, the aortic valve opens and the blood is pumped into the aorta. At the beginning of the ejection phase blood pressure still rises but begins to decline when the majority of the blood has left the ventricle. As soon as the left ventricular pressure drops below the aortic pressure, the aortic valve will be closed. This event demarcates the end of the systole and the beginning of diastole. The diastolic phase begins with a rapid isovolumic relaxation leading to a drop of left ventricular pressure below the atrial pressure. In consequence, the mitral valve opens for filling of the left ventricle. The early phase of filling is a passive event; the later phase, however, is mediated by atrial contraction.

Cellular Composition

On a cellular scale, cardiac myocytes (CMs), interstitial fibroblasts, and capillary endothelial cells represent the major cell fractions of the heart (Fig. 1). Moreover, the coronary arteries and veins contribute smooth muscle and endothelial cells to the cardiac cell pool.

A. Gödecke
Heinrich-Heine-Universität Düsseldorf,
Institut für Herz- und Kreislaufphysiologie,
Building 22.03., Floor 00, Universitätsstr. 1,
Düsseldorf 40225, Germany
e-mail: axel.goedecke@uni-duesseldorf.de

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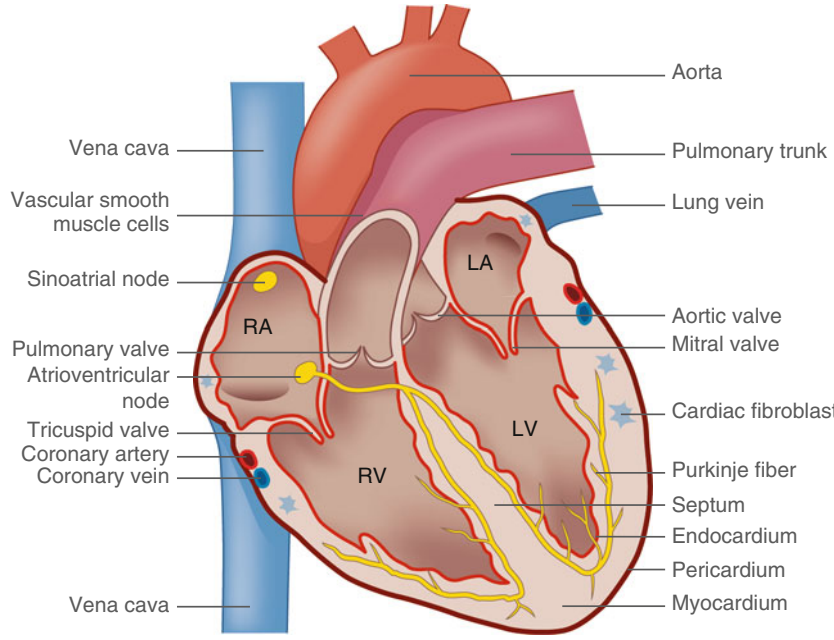

Fig. 1 Anatomic features of the human heart

CMs represent the major cell type in terms of mass and dominate the structure of the myocardium. CMs show a characteristic striated pattern similar to skeletal muscle, which is due to the parallel organization of the contractile actin and myosin filaments. At their ends, CMs are connected via intercalated discs. These structures are rich in gap junctions, which allow the spreading of the electric excitation over the myocardium due to a direct electric coupling of CMs. A highly coordinated sequence of temporal and spatial excitation and contraction of CMs leads to a continued cycle of ventricular contraction and relaxation of the whole heart.

Interstitial and perivascular fibroblasts account for two thirds of cardiac cells in terms of numbers [1]. Cardiac fibroblasts synthesize the extracellular matrix, which provides an extracellular protein scaffold for the attachment of CMs, fibroblasts, and endothelial cells. The amount and composition of the cardiac extracellular matrix are important determinants of myocardial stiffness. Therefore, activation of cardiac fibroblasts and enhanced matrix deposition which occur during aging but also in the context of heart failure (see chapter "Heart failure") may lead to a reduced ventricular compliance, which impedes diastolic filling.

Endothelial cells also form the inner cell layer of the cardiac chambers termed endocardium. Finally, the heart is surrounded by the pericardium, protecting this vital organ.

The heart is supplied by its own circulatory system, which originates at the aortic root in the form of two main coronary arteries. Since the heart critically depends on aerobic metabolism, there is an extraordinary high capillary density within the myocardium [2].

Cardiac Muscle Contraction

The heartbeat is the consequence of a well-defined temporal and spatial sequence of excitation and contraction of the cardiac muscle. The origin of the electric excitation is the sinoatrial node (SA node), which consists of specialized CMs able to depolarize spontaneously and autonomously. The SA node represents the primary pacemaker of the heart, and upon its depolarization, a wave of depolarization spreads over the atria. The atrioventricular plane which is assembled by the heart valves insulates the ventricles from the atria. The only conducting connection is the atrioventricular node (AV node), which is

located in the right atrial septum. The atrial excitation passes the AV node and is then conducted to all regions of the ventricular walls by the specialized CMs forming the conduction system including the bundle of His, branches of Tawara, and the Purkinje fibers. The final step of ventricular excitation involves the conduction between CMs via gap junctions.

Due to an unstable resting potential, SA nodal cells depolarize spontaneously, and the SA node is able to initiate cardiac excitation autonomously. However, the slope of this diastolic depolarization is increased by noradrenaline released by sympathetic nerve fibers, which elevates heart rate (positive chronotropy). Acetylcholine, the parasympathetic transmitter, reduces heart rate by flattening the slope of diastolic depolarization. By similar mechanisms, sympathetic innervation of the AV node increases the AV conduction time (positive dromotropy) whereas acetylcholine decreases it (negative dromotropy).

Heart-Specific Metabolic/Molecular Pathways and Processes

With more than three billion contractions, the heart pumps more than 200 million l of blood through the vasculature during a normal human life span. In order to continuously perform its function, the heart critically depends on oxidative phosphorylation. Therefore, delivery of oxygen via coronary perfusion must tightly match cardiac oxygen demands even under high workload. As cardiac muscle contains only around 5 μmol ATP/g wet weight, all ATP would be consumed within 10 s if oxidative ATP generation was stopped.

Almost 95 % of cardiac ATP generation occurs through oxidative phosphorylation, which represents the most efficient way to generate ATP. This high level of oxidative phosphorylation is reflected by a high mitochondrial content (30–35 Vol %) in the CMs. Glycolysis produces most of the residual ATP (<5 %).

Most ATP (60–70 %) is spent in CMs to generate mechanical work driving the circulation. Another large part (30–40 %) is required to run ion pumps (mostly sarco-/endoplasmic reticulum Ca^{2+}-ATPase), which in a concerted manner generate the Ca^{2+} transients [3]. The periodic release and reuptake of Ca^{2+} are required for electromechanical coupling, linking cardiac action potentials with contraction. When the membrane potential of a CM reaches the threshold (−70 mV), opening of voltage-gated sodium channels depolarizes the membrane potential to +30 mV followed by the opening of L-type Ca^{2+} channels which mediate an influx of Ca^{2+} from the interstitial space. This Ca^{2+} current serves dual functions. First, it leads to a long-lasting (200–400 ms) depolarization at a voltage around 0 mV before K^+ conductivity reverses the membrane potential back to the diastolic values (−90 mV). Second, the Ca^{2+} influx gives rise to further Ca^{2+} release from intracellular stores by opening the ryanodine channel (Ryr2) in the membrane of the sarcoplasmic reticulum (SR). Finally, the intracellular Ca^{2+} concentration increases to 10^{-5} mol/l (from initially 10^{-7} mol/l). Subsequent Ca^{2+} binding to troponin C displaces tropomyosin from actin, enabling myosin to bind and to perform contraction. This is terminated by Ca^{2+} reuptake into the SR and via export by the sarcolemmal Na^+/Ca^{2+} exchanger.

Sympathetic nerve fibers also innervate the myocardium. Norepinephrine increases Ca^{2+} influx, release from the SR, and accelerates reuptake into the SR leading to faster and increased Ca^{2+} transients, which are the basis for enhanced contractile force (positive inotropy).

As only a minor part of the ATP is required for basal biochemical reactions, an experimentally arrested heart consumes only 10 % of the oxygen required to run a working heart. The high demand for ATP of a beating heart even under resting conditions results in a high degree of oxygen demand. The heart consumes 10 % of the whole-body oxygen, although it contributes only 0.5 % to whole-body mass. The high rate of oxygen consumption leads to low PO_2 values in cardiac tissues. The resultant steep O_2 gradient toward the capillaries favors oxygen release from hemoglobin and results in a high oxygen extraction (60–70 %) from the perfused blood already under basal conditions. Thus, the elevated oxygen demand under conditions of high workload can

be covered only to a small part by an increase in oxygen extraction (+20 %). Instead, an increase in coronary flow (up to fivefold) largely ensures cardiac oxygen supply to sustain the oxidative generation of ATP.

Cardiac Substrate Metabolism

Cardiac substrate metabolism occurs in two major variants: The fetal heart depends to a large extent on glucose, whereas the adult heart prefers to consume fatty acids rather than glucose. However, the heart is also able to metabolize lactate and ketone bodies. Therefore, the adult heart has often been named a "metabolic omnivore." All substrates may finally drain into the citric acid cycle that is fueled by acetyl-CoA derived from glycolysis (glucose), β-oxidation (fatty acids), lactate oxidation, and ketone bodies. Interestingly, in heart failure (see chapter "Heart failure"), the adult heart may reduce fatty acid oxidation in favor of glucose (termed metabolic remodeling) [4].

Fatty acids account for 50–70 % of total cardiac energy supply in adults. Fatty acid uptake into CMs is mediated to a large extent by fatty acid translocase (FAT/CD36). This protein is in part localized in storage vesicles in CMs, which may fuse with the sarcolemma to enhance uptake of fatty acids (Fig. 2). Important stimuli of membrane translocation are an increase in cardiac workload (contraction-mediated translocation) and insulin. Fatty acids are further oxidized in the mitochondria during β-oxidation yielding high amounts of $NADH + H^+$, $FADH_2$, and CO_2. Transport of acyl-CoA into the mitochondrion involves the carnitine shuttle system (Fig. 2).

Glucose uptake by CMs may be stimulated under anabolic conditions by insulin via Akt (also called protein kinase B) and under catabolic conditions by the AMP-dependent protein kinase. Both stimulate translocation of the glucose transporter 4 (GLUT4) to the sarcolemma, enhancing glucose uptake (Fig. 2). In part, glucose is used to synthesize glycogen, which serves as an energy store. Upon energy depletion and activation of AMP-dependent protein kinase, glucose is rapidly mobilized by breakdown of glycogen [5]. Independent of its origin, most glucose enters the glycolytic pathway, leading to the formation of pyruvate.

Lactate also contributes to cardiac ATP generation. It is taken up by the monocarboxylate transporter and converted to pyruvate by the lactate dehydrogenase reaction yielding $NADH + H^+$. The latter enters the respiratory chain, whereas pyruvate is oxidized to acetyl-CoA. Even under conditions of elevated workload, the heart rather consumes than generates lactate. Thus, during exercise, the heart may use lactate produced by anaerobic glycolysis in skeletal muscle.

Inside-In: Metabolites of the Heart Affecting Itself

A hallmark of cardiac metabolism is the ability to switch between carbohydrates and fatty acids as preferred carbon sources (metabolic flexibility). Under conditions when oxygen is short, the heart uses more "oxygen-rich" glucose, which results in a higher P/O ratio (ATP per oxygen) than the use of the "oxygen-poor" fatty acids.

An important pathway is the Randle cycle [6, 7], also termed the glucose–fatty acid cycle, which is substantially involved in regulating the relative contribution of fatty acid vs. carbohydrate utilization by the heart. Pyruvate, acetyl-CoA, malonyl-CoA, and citrate are important metabolic intermediates, which modulate substrate utilization (Fig. 2).

Fatty acid oxidation increases the mitochondrial acetyl-CoA/CoA and $NADH/NAD^+$ ratios. These changes inhibit pyruvate dehydrogenase (PDH), which determines the oxidation of the glycolytic pyruvate to acetyl-CoA. The activity of PDH is controlled by PDH kinases and PDH phosphatases (Fig. 2). In addition, citrate, leaving mitochondria via citrate carriers, inhibits phosphofructokinases 1 and 2 and therefore reduces glycolysis. However, cytoplasmic citrate can also be converted to acetyl-CoA (and oxaloacetate), which is further converted to malonyl-CoA. Malonyl-CoA inhibits the carnitine shuttle system and thereby long-chain fatty acid uptake by mitochondria.

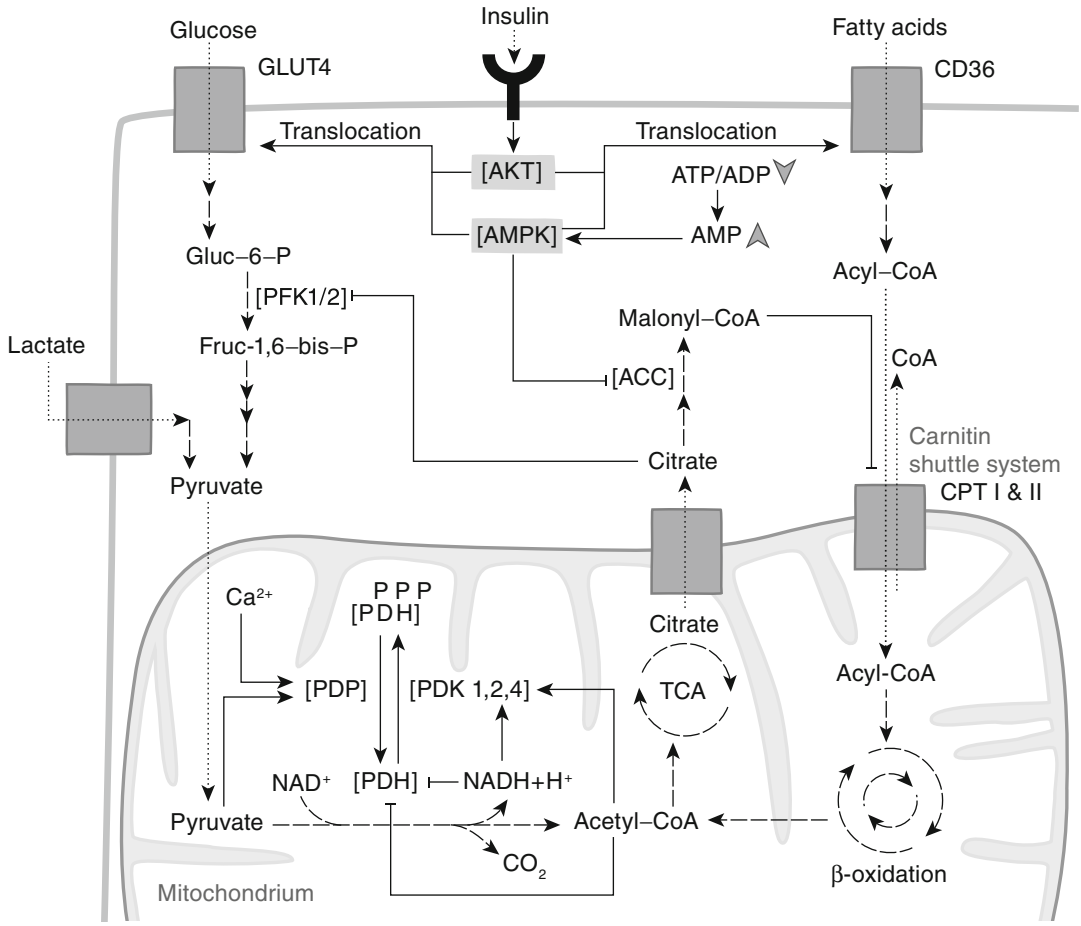

Fig. 2 Regulation of glucose and fatty acid metabolism in the heart. The basic principle of the glucose fatty acid cycle and its modulation by insulin and low energy is shown. A low ATP/ADP ratio leads to formation of AMP, which activates AMP-dependent protein kinase (*AMPK*). Insulin activates protein kinase B (*AKT*) via the insulin receptor. AKT and AMPK induce translocation of the glucose transporter 4 (*GLUT4*) and the long-chain fatty acid translocase (*CD36*) to the plasma membrane. Glucose is metabolized in glycolysis (*left*) to pyruvate, which is subsequently oxidized to acetyl-CoA by pyruvate dehydrogenase (*PDH*) in the mitochondrion. PDH underlies product inhibition by acetyl-CoA and NADH + H^+ from the β-oxidation. Additionally, they stimulate specific PDH kinases (*PDKs*), which inhibit PDH by phosphorylation. PDH phosphatase (*PDP*) dephosphorylates and thus activates PDH. PDP is activated by pyruvate and Ca^{2+}, linking mean elevated cytoplasmic Ca^{2+} under β-adrenergic stimulation to elevated glucose oxidation. Lactate is also converted to pyruvate. Fatty acids are converted to acyl-CoA and transported to the mitochondrion via the carnitine shuttle system consisting of carnitine palmitoyltransferase (*CPT*) I and II, in the outer and inner mitochondrial membrane, respectively. Within the mitochondrion, acyl-CoAs are degraded to acetyl-CoA during β-oxidation. Acetyl-CoA is metabolized in the tricarboxylic acid cycle (*TCA*, also called citric acid cycle). Citrate from the TCA can be exported to the cytosol, where it inhibits early steps of glycolysis and can be converted to malonyl-CoA. The latter inhibits the carnitine shuttle system and thus fatty acid oxidation. AMPK was shown to inhibit this conversion by blocking Acetyl-CoA carboxylase (*ACC*). *Fruc-1,6-bis-P* fructose-1,6-bisphosphate, *PFK1/2* phosphofructokinase 1/2

In the heart, the transport capacity of GLUT4 transporters is almost saturated at physiological plasma glucose levels limiting glucose inflow and thus glycolytic flux. Stimulation of GLUT4 translocation (see above) elevates glycolytic flux and increases pyruvate, releasing the blockade of PDH by PDH phosphatases (Fig. 2). In consequence, glucose metabolism is elevated despite

the presence of fatty acids. However, the precise interplay of metabolic factors directing cardiac metabolism toward one or the other direction is still not fully understood [8].

The extent of metabolic remodeling is substantially modulated by comorbidities such as diabetes, hypertension, hypercholesterolemia, etc. Thus, identification of the master switches directing cardiac metabolism toward a protective program is of high medical importance.

Further important metabolites released by the heart are nitric oxide (NO) and adenosine. Both of them are only short-lived and exert local functions. These include modulation of coronary vascular tone and cardiac contractility (see below). Moreover, NO and adenosine are able to keep platelets and leukocytes in a quiescent state, acting as antithrombotic and anti-inflammatory factors.

In the heart, NO, which is derived from L-arginine, is synthesized in the coronary endothelium by the endothelial NO synthase (type III NOS). In CMs, the endothelial as well as the neuronal NO synthase (type I NOS) are constitutively expressed. Under inflammatory conditions, also the inducible NO synthase (type II NOS) may be upregulated. NO modulates cardiac contractile function, and depending on the NO concentrations, both positive as well as negative inotropic actions have been described. The underlying mechanism appears to involve modulation of Ca^{2+} homeostasis as well as the availability of cAMP due to the modulation of phosphodiesterases. NO-mediated vasodilation involves a direct activation of the soluble guanylyl cyclase, elevation of cGMP, and activation of the cGMP-dependent protein kinase (PKG). PKG in turn activates the myosin light chain phosphatase by phosphorylation, which leads to a dephosphorylation of the regulatory myosin light chain in smooth muscle cells and the concomitant reduction of vascular tone.

Besides NO derived from NOS, recent studies suggest that under hypoxic conditions, deoxygenated hemoglobin and myoglobin reduce circulating nitrite to NO. This interesting concept provides a link between cardiac ischemia and the vasodilatory and cardioprotective functions of NO [9].

Under hypoxic or ischemic conditions, ATP breakdown may lead to the formation of adenosine. Adenosine released from the myocardium or formed extracellularly from ATP is able to elevate cardiac perfusion by the activation of smooth muscle cell A_2A receptors and subsequent enhancement of cAMP. cAMP in turn stimulates PKA, which phosphorylates and thereby inhibits the regulatory myosin light chain kinase and stimulates MLC phosphatase, leading to relaxation. Moreover, activation of K_{ATP} channels via PKA-mediated phosphorylation may lead to hyperpolarization of smooth muscle cells and therefore vasodilation. The cardiac release of adenosine is minimal as long as oxygen supply is sufficient to match the demands [10]. Therefore, in contrast to NO, which is important for the setting of the basal vascular tone, adenosine-mediated vasodilation is more important under hypoxic conditions.

Inside-Out: Metabolites of the Heart Affecting Other Tissues

In the context of inside-out signaling, peptide factors released by the heart act on other organs. The natriuretic peptides (NPs), atrial and brain NP, which are expressed predominantly in the atria and the ventricles, respectively, are released from the heart in response to mechanical signals such as stretch and elevated mechanical load, e.g., during volume overload or exercise. They activate membrane-bound guanylyl cyclase receptors, which elevate cGMP levels in target cells and regulate fluid homeostasis and reduce blood pressure via increased Na^+ excretion (see chapter "Overview" under part "Kidney"). However, recent results indicate that natriuretic peptides also have an important metabolic function. NP receptors are present on adipocytes and their activation stimulates lipolysis. Interestingly, the potency of NP to enhance lipolysis is similar to that of β-adrenergic stimulation, which represents the classical way. Whereas the latter is mediated by the cAMP–PKA pathway, NPs exert their effects via cGMP and PKG. The physiological role of this pathway can be seen in an elevated supply of heart and skeletal muscle with fatty

acids during exercise, when mechanic forces stimulate the release of NP from the heart [11].

It is well known that heart failure (see chapter "Heart failure") may be associated with the loss of skeletal muscle. This interconnection of cardiac dysfunction and skeletal muscle wasting has been termed cardiac cachexia. Chronic heart failure leads to upregulation of myostatin expression in cardiac tissue. Myostatin, a cytokine of the transforming growth factor (TGF)-β family, inhibits muscle development and might be involved in cardiac cachexia. Exercise reduces myostatin expression, whereas physical inactivity may enhance it. The mechanisms by which myostatin leads to atrophy of skeletal muscle involves a reduced avtivation of protein kinase B (AKT), which might diminish protein synthesis via low mTOR activity or enhance protein degradation via induction of atrogin-1.

Outside-In: Metabolites of Other Tissues Affecting the Heart

Elevated levels of circulating free fatty acids (FFA) may affect cardiac structure and function in several ways [4]. In rodent models, the elevated uptake of fatty acids, frequently associated with insulin resistance, leads to the development of cardiac lipotoxicity characterized by contractile dysfunction, CMs apoptosis, and fibrosis. An enhanced FFA uptake may increase the cardiac stores of triacylglycerol or triglyceride (TG). Enhanced deposition of TG in the myocardium results in cardiac steatosis, i.e., the ectopic deposition of surplus fatty acids in the form of TG in CMs. The enhanced availability and metabolism of TG also elevate ceramide levels in the heart. Ceramides have been shown to induce apoptosis of CMs by enhancing mitochondrial permeability. Moreover, ceramides inhibit Akt, which are involved in cellular metabolism, growth, and survival. On the other hand, elevated TGs also enhance diacylglycerol known to activate conventional and novel PKC isoforms [12], which may be protective or pathologic. Among the latter, PKCβ1 was shown to phosphorylate the β subunit of the insulin receptor as well as insulin receptor substrate 1 (IRS1) on multiple serine/threonine residues thus contributing to insulin resistance.

Also, enhanced glucose levels can have detrimental effects on cardiac function. For example, hyperglycemia enhances diacylglycerol formation and activation of PKC. Interestingly, in the presence of high fatty acid levels, glucose oxidation is blocked. Glucose is redirected to other pathways including the pentose phosphate pathway, which leads to synthesis of NADPH required for the formation of glutathione, an important antioxidant.

Final Remarks

The healthy heart is a metabolic omnivore, which is able to utilize carbon sources including glucose, lactate, ketone bodies, and fatty acids for oxidative generation of ATP. The hypertrophic and failing heart, respectively, switch their metabolism from the usually preferred fatty acids to higher glucose consumption. Although still not unambiguously clarified, many experimental studies indicate that this metabolic remodeling is an important mechanism contributing to adaptation during the compensated state in heart failure progression and encourage to develop metabolic therapies to treat heart failure [13].

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