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Review

# Nutrient sensing and utilization: Getting to the heart of metabolic flexibility

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ABSTRACT

A central feature of obesity-related cardiometabolic diseases is the impaired ability to transition between fatty acid and glucose metabolism. This impairment, referred to as "metabolic inflexibility", occurs in a number of tissues, including the heart. Although the heart normally prefers to metabolize fatty acids over glucose, the inability to upregulate glucose metabolism under energetically demanding conditions contributes to a pathological state involving energy imbalance, impaired contractility, and post-translational protein modifications. This review discusses pathophysiologic processes that contribute to cardiac metabolic inflexibility and speculates on the potential physiologic origins that lead to the current state of cardiometabolic disease in an obesogenic environment.



**Contents**



## 1. Introduction

Organismal metabolism is among the most highly regulated processes in biology. Maintaining metabolic homeostasis is challenging due to the variation in food availability, diet composition,

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and caloric content of dietary macronutrients (i.e., carbohydrates, fat, and protein). Consequently, precise nutrient sensing and utilization is necessary for coordinating multiple organ systems to regulate metabolic balance. Organisms accomplish this by continuously monitoring and producing neurochemical signals and circulating soluble factors that function across a range of timescales, tissues, and cell types. A central feature of obesity and age-related chronic diseases, such as diabetes and heart disease, is the impaired regulation of how macronutrients are sensed and metabolized. In particular, aging and obesity are associated with the development of insulin resistance and adipose tissue accumulation [1]. At the cellular level, these changes are associated with an impaired ability to transition between the utilization of different macronutrients (e.g. glucose versus fat) to meet biosynthetic and bioenergetic demands. This impairment is generally referred to as "metabolic inflexibility" and is considered a central pathologic feature of chronic metabolic diseases [2].

The goal of this review is to discuss the physiologic and pathophysiologic mechanisms involved in the regulation of glucose versus fatty acid oxidation. Multiple organ systems, such as the liver, brain, skeletal muscle, pancreas, and adipose tissue, are involved in this process. Here, we focus on the role of the heart as both a target and contributor to the metabolic inflexibility that occurs with aging and obesity. We discuss recent research about how changes in neuroendocrine and redox-sensitive signaling pathways impair macronutrient sensing and oxidation under physiologic and pathophysiologic conditions. We also discuss the role of reversible post-translation mitochondrial protein modifications and reactive oxygen species (ROS) as intra- and intercellular mediators of cardiac function and metabolism. Finally, we review intriguing new findings that suggest that the heart itself is the source of secreted soluble factors—"cardiokines"—that contribute to the overall regulation of whole body metabolism. These findings also highlight cardiac regulatory pathways that are shared between mammals and more evolutionarily distant model organisms, such as *Drosophila*. An improved understanding of the evolutionary origins of how glucose and fatty acid metabolism are regulated may help to develop new dietary and therapeutic strategies to improve cardiovascular function and overall health as we age.

### 1.1. Metabolic inflexibility and cardiac pathophysiology

Cardiac output is an energetically demanding process, accounting for approximately 10–20% of whole-body metabolic demand during resting conditions [3]. The heart derives energy primarily from the oxidation of fatty acids. Non-hormonal mechanisms ensure that when both glucose and fatty acids are present, the heart preferentially uses fatty acids. This phenomenon, first noted by Randle in 1963, ensures that fatty acid oxidation reduces glucose utilization [4]. It occurs through an elegant series of allosteric inhibitions that became known as the Randle Cycle. The general biochemical outcome of the Randle cycle is to conserve glucose for the brain in the absence of food or to enhance glycogen synthesis in the muscles after feeding [4–7]. While this glucose-sparing phenomenon has a strong role in survival during times of nutrient deprivation, it becomes problematic in today's world with the epidemic rise in obesity and diabetes, which limit the metabolic flexibility to oxidize glucose during periods of enhanced energetic demands.

Prolonged reliance on fatty acid oxidation that occurs as a result of diets high in fat content results in obesity, diabetes, and cardiac pathologies. For example, mice that exclusively rely on fatty acid oxidation induced by diabetes [8], peroxisome proliferator-activated receptor (PPAR) overexpression [9], or phosphofructokinase-2 (PFK-2) deficiency [10], develop lipotoxicity and cardiac hypertrophy. In the case of diabetes, this metabolic inflexibility contributes to diabetic cardiomyopathy [11]. In fact, paradoxically, starvation also elevates levels of circulating fatty acids that, in turn, increase the utilization of fatty acids relative to glucose for energy production in multiple tissues [12–17]. Thus, the dilemma with such metabolic conditions is that the Randle cycle functions not only as a glucose-sparing phenomenon, but rather a feed forward mechanism to increase cardiac metabolic inflexibility.

Maintaining dynamic glucose utilization in the presence of fatty acids is essential for optimal cardiac function. For example, the heart rapidly oxidizes glucose following β-adrenergic stimulation to supply ATP during increased cardiac output. The dynamic capacity to increase glucose utilization is also necessary for the heart to recover from pathophysiological metabolic stresses, such as ischemia/reperfusion [13]. Thus, understanding the mechanisms by which the heart overrides the Randle cycle may be one approach to developing therapeutic targets to promote metabolic flexibility and thereby minimize cardiomyopathies associated with increased dietary fat, obesity, and diabetes. For such a strategy, it is important to consider the metabolic factors that contribute to the Randle cycle. The increase of acetyl CoA, citrate, and NADH generated by fatty acid oxidation inhibits the oxidation of glucose at two key regulatory points (Fig. 1). When fatty acids are oxidized, an increase in the Krebs cycle intermediate, citrate, inhibits PFK-1, which is the first committed and rate limiting step in glycolysis [18]. The mitochondrial enzyme pyruvate dehydrogenase (PDH) is also central to regulating the use of glucose relative to fatty acids for energy homeostasis. PDH commits glycolytically-derived pyruvate for ATP production [19–21]. PDH is regulated by various isoforms of pyruvate dehydrogenase kinase (PDK1, 2, 3, 4) and phosphatase (PDP1 and 2), with phosphorylation resulting in enzyme inhibition. Products of fatty acid oxidation (NADH and acetyl-CoA) activate PDKs resulting in PDH phosphorylation and inhibition [19–21]. Thus, when fatty acids are available, the intrinsic capacity to utilize glucose is low. Understanding how the heart normally overrides the Randle cycle provides both opportunities and challenges for restoring cardiac metabolic flexibility.

### 1.2. Sympathetic stimulation of glycolytic flux: targeting PKA

The autonomic nervous system, comprised of the sympathetic and parasympathetic systems, is the primary means of regulating cardiac output and coordinating the moment-to-moment changes in contractile demand with commensurate changes in metabolism. The effects of the sympathetic stimulation are mediated by β-adrenergic receptors and the downstream production of cyclic AMP (cAMP) (Fig. 1). The main intracellular target of cAMP is cyclic AMP dependent protein kinase (PKA). Activation of PKA concertedly increases cardiac contractility and metabolism via the phosphorylation of specific protein substrates that enhance $Ca^{2+}$ cycling [22]. Thus, activation of the β-adrenergic pathway is an efficient mechanism of coordinating appropriate metabolic and biomechanical responses to rapid increases in contractile demands and acute stresses.

The primary means of increasing glycolytic flux upon sympathetic stimulation is via the activation of PFK-2, a bifunctional enzyme containing both kinase and phosphatase activities that produces and degrades fructose-2,6-bis-phosphate, respectively [23,24]. This metabolite is a potent activator of PFK-1, a rate-limiting step of glycolysis. The catalytic activity of PFK-2 is regulated by its phosphorylation state [25]. Phosphorylation of the heart isoform of PFK-2 (PFKFB2) increases its kinase activity and production of fructose-2,6-bis-phosphate. With sympathetic stimulation, PKA mediates the phosphorylation and activation of PFK-2