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The Effects of Ketone Body Metabolism at Different Rates and Concentrations on Mitochondrial Function and Cardiomyopathies

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Abstract. Ketone bodies are a group of small water-soluble molecules produced during metabolism, mainly acetoacetate (AcAc),β-hydroxybutyrate (βOHB), and acetone. Ketone bodies are processed through evolutionarily conserved pathways that help keep energy balance, especially in tissues with high energy demand such as the brain, heart, and skeletal muscle when carbohydrate availability is low. Attention to ketone body metabolism has grown in recent years, as clinical studies are now exploring strategies such as intermittent fasting, low-carbohydrate ketogenic diets, and using exogenous ketone supplements. These approaches are being tested for their potential to improve overall health, prevent or treat disease, and slow down the effects of aging.As the production and utilization of ketone bodies both take place in mitochondria, and ketone bodies are closely related to the cardiomyocytes This review aims to investigate differences in the impact of varying ketone body metabolism rates and ketone body concentrations on mitochondria in cardiomyocytes and the common pathological processes of cardiomyopathy.

Keywords: Ketone body metabolism, Mitochondria, Cardiomyopathy

1. Introduction

In the 20th century, the idea that ketone bodies were just metabolic waste was revised. Ketone bodies significantly contribute to mammalian energy metabolism during fasting, exercise, the neonatal phase, pregnancy, or when consuming a diet low in digestible carbohydrates and high in fat [1]. When carbs are scarce, ketone bodies help maintain bioenergetic balance, notably in the heart, brain, and skeletal muscle [2]. Apart from that, it has become evident that ketone bodies also have signalling functions; for example, βOHB works as an endogenous inhibitor of HDACs [3].

Multiple studies link cardiomyopathy to altered cardiac metabolism, where energy metabolism disruptions can induce the condition. Both metabolic and bioenergetic evidence suggest that ketone body metabolism may play a crucial role in the myopathic heart [2]. Since ketone bodies act as both a metabolic substrate and a signalling molecule in heart disease [4], it is crucial to study ketone body metabolism, and it is significant. Ketone bodies both originate and break down in mitochondria [5]. As a result, exploring the connection between ketone bodies and mitochondria is essential for the investigation of ketone body metabolism. The significance of this study is to understand the positive

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and negative impacts of different ketone body concentrations and different ketone body metabolism rates on mitochondria in cardiomyocytes and the common pathological processes of cardiomyopathy. Additionally, it can provide a reference for future researchers.

2. Ketone body metabolism

2.1. Processes and products of ketone body metabolism

Ketone body metabolism mainly involves ketogenesis, ketone body transport, and ketone body utilization.

Ketone bodies, synthesized by the liver, include AcAc, βOHB, and acetone. When carbohydrates are scarce, 3-hydroxymethylglutaryl-CoA synthase 2, encoded by Hmgcs2, catalyzes a key ketogenic step by condensing β-oxidation–derived acetoacetyl-CoA and acetyl-CoA to form HMG-CoA, which HMGCL then breaks down to produce AcAc [2]. βOHB is synthesised through the mitochondrial reduction of AcAc [6]. Phosphatidylcholine-dependent mitochondrial D-β-hydroxybutyrate dehydrogenase (BDH1) catalyses an NAD^+/NADH-linked reaction that operates close to equilibrium, with the Keq favouring the formation of βOHB [2]. At the same time, acetone is produced by the spontaneous decarboxylation of AcAc [7].

Ketone bodies synthesized in the liver are exported from hepatocytes into the bloodstream via solute carriers SLC16A1, SLC16A6, and SLC16A7, which are monocarboxylate transporters, thereby entering the systemic circulation [8]. Monocarboxylate transporters also play a crucial role in the uptake of ketone bodies. Ketone bodies are imported into extrahepatic tissues through the transporters SLC16A1 and SLC16A7. BDH1 in mitochondria catalyzes βOHB oxidation to AcAc, which SCOT then converts to AcAc-CoA. SCOT, the sole mammalian CoA transferase, facilitates a near-equilibrium CoA transfer between succinate and AcAc. AcAc-CoA hydrolysis releases more free energy than succinyl-CoA hydrolysis. Therefore, coenzyme A favours combining with AcAc. AcAc-CoA is then cleaved by mitochondrial thiolase (mThiolase) in a reversible reaction to generate two molecules of acetyl-CoA, which subsequently enter the tricarboxylic acid (TCA) cycle to provide energy [2].

2.2. Factors affecting the rate of ketone body metabolism

Ketone bodies are mainly synthesized in the liver from acetoacetyl-CoA and acetyl-CoA derived through fatty acid β-oxidation. Consequently, the amount of fatty acids used and the intensity of β-oxidation directly determine the rate of ketone body production. When carbohydrate availability is limited, such as fasting or a low-carbohydrate diet, enhanced fat mobilization leads to increased acetoacetyl-CoA and acetyl-CoA generation via β-oxidation, thereby driving a higher hepatic ketogenesis rate.

As mentioned earlier, HMGCS2 is the key enzyme in ketone body synthesis, whereas SCOT is the essential enzyme for ketone body oxidation in extrahepatic tissues. So, their activity and concentration can influence the rate of ketone body metabolism.

3. Impact of ketone body metabolism on mitochondrial function in cardiomyocytes

3.1. Main functions of mitochondria in the myocardium

In cardiomyocytes, mitochondria generate about 90% of ATP, are densely arranged within a highly complex structure and occupy 30% of the cell's volume [9].

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The inner membrane of mitochondria folds into numerous structures known as cristae, the central sites of ATP production. In adult cardiomyocytes, cristae are especially dense because of the heart's continuous demand for energy to sustain contraction. Furthermore, these cristae exhibit dynamism, undergoing rapid fusion and division in response to fluctuating energy demands, thus optimizing ATP production [9]. Besides, alterations in mitochondrial morphology may vary mitochondrial function and, in turn, impact overall cellular function. A key characteristic of mitochondria, particularly in cardiomyocytes, is regulating energy production within the intermembrane space, carried out by various phosphotransfer enzyme systems.

3.2. Impact of abnormally low or high ketone body metabolism rate and concentration on mitochondria

At moderate concentrations, ketone bodies serve as efficient energy substrates, yielding more ATP than glucose while requiring less oxygen per molecule compared to fatty acid oxidation [10]. This metabolic efficiency lowers the oxidative burden on mitochondria. It helps improve the state of energy deficiency, as seen in heart failure, where myocardial mitochondria increase ketone utilization to offset impaired fatty acid oxidation. Furthermore, βOHB inhibits NLRP3 inflammasome activation, diminishing inflammatory cytokine release and safeguarding mitochondria against inflammatory damage [11]. For example, in models of myocardial ischemia, ketone bodies mitigate mitochondrial swelling and cristae disruption through this mechanism.

However, ketone bodies are known to cause ketosis or ketoacidosis when excessively accumulated, which may cause fatal consequences. During ketoacidosis, excessive accumulation of βOHB and AcAc lowers intracellular pH. Mitochondrial matrix acidification inhibits the TCA cycle and oxidative phosphorylation, reducing ATP production and causing dysfunction. Moreover, excessive ketone body oxidation produces a lot of NADH. The mitochondrial respiratory chain cannot reoxidize it back into NAD^+ in time, leading to a lack of NAD^+. This shortage of NAD^+ then blocks the TCA cycle and mitochondrial autophagy, hindering the removal of damaged mitochondria and creating a vicious cycle.

In Hmgcs2 knockout mice, the disruption of ketone body synthesis leads to acetyl-CoA accumulation in mitochondria, resulting in minimal ketone production [12]. When the concentration of ketone is low, excess acetyl-CoA can act as an acetyl donor, leading to abnormal acetylation modification of mitochondrial proteins (such as TCA cycle enzymes and oxidative phosphorylation complexes), inhibiting their enzymatic activity and directly impeding mitochondrial energy metabolism.

4. Impact of ketone body metabolism on cardiomyopathy

4.1. Etiology and symptoms of cardiomyopathy

Cardiomyopathies involve structural and functional heart muscle abnormalities, from cellular changes to heart failure and arrhythmias [13].

Cardiomyopathy can be divided into primary and secondary categories. Primary cardiomyopathy, whose lesions are mainly confined to the heart, is classified by etiology into genetic, acquired, and mixed types [13]. The genetic type includes hypertrophic cardiomyopathy, which arises from chromosomal abnormalities or gene mutations. For example, hypertrophic cardiomyopathy is linked to autosomal dominant mutations that affect genes encoding sarcomeric proteins. The acquired type comprises non-genetic factors, such as myocarditis, perinatal physiological changes, long-term

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effects of tachycardia, and severe emotional or physical stress, which trigger peripartum cardiomyopathy, Takotsubo cardiomyopathy and acquired cardiomyopathy. Additionally, the mixed type contains dilated and restrictive cardiomyopathy. Mixed cardiomyopathy, meanwhile, has etiologies involving both genetic and non-genetic factors.

Secondary cardiomyopathy stems from systemic diseases, including endocrine (e.g., diabetes, thyroid disorders), infectious (viral, bacterial, parasitic), toxic (alcohol, chemotherapy, heavy metals), and autoimmune (e.g., rheumatoid arthritis) etiologies.

Cardiomyopathy presents diverse forms and origins, yet common types often manifest similar symptoms [13]. Hypertrophic, dilated, and restrictive cardiomyopathy can all show symptoms typically seen in heart failure with reduced ejection fraction, such as fatigue, peripheral edema, orthopnea, exertional dyspnea, paroxysmal nocturnal dyspnea, presyncope, syncope, and cardiac ischemia. Some patients may experience symptoms such as chest pain and palpitations associated with arrhythmias.

4.2. Common pathological processes of cardiomyopathy

There are many standard pathological processes in cardiomyopathy—for example, cardiomyocyte hypertrophy. Ventricular cardiomyocytes enlarge under altered contractility or physiological stress, increasing wall thickness and reducing chamber size [14]. Regardless of the initial trigger, cardiac hypertrophy is generally considered a compensatory response because it can restore the increased pressure on the ventricular wall to normal and enhance the heart's ability to contract.

In another pathological state, heart muscle cells re-express genes from the embryonic stage, such as natriuretic peptides (ANF, BNP), beta-myosin heavy chain (β-MyHC), and α-skeletal actin. This stage is called abnormal activation of the fetal genetic program [14]. Initially, sustained gene activation attempts to preserve cardiac function via hemodynamic regulation (e.g., diuresis, vasodilation), but prolonged expression exacerbates pathology, indicating cardiomyopathy.

Then, in a normal adult heart, β-MyHC makes up more than 90% of myosin heavy chains. However, in disease conditions, its expression is further elevated, concurrent with a reduction in α-MyHC [14]. β-MyHC has low ATP enzyme activity and slow filament sliding speed. This leads to a drop in the heart muscle's contractile force and shortening speed.

Fibrosis in the interstitium and around blood vessels is the key pathological feature of cardiomyopathy [14]. Cardiac fibroblasts and some cardiomyocytes mainly cause it, secreting type I and III collagen. Fibrosis damages the excitation-contraction coupling between cardiomyocytes, increases the stiffness of the heart muscle, and directly reduces cardiac contraction and relaxation function.

4.3. Impact of abnormally low or high ketone body metabolism rate and concentration on cardiomyopathy

When the rate of cardiac ketone body metabolism is too low, it will aggravate pathological remodelling. The heart cannot use ketones as an energy source under stress overload. This leads to increased production of reactive oxygen species (ROS) and mitochondrial and myofibril ultrastructure disruption. In practice, four weeks after pressure overload–induced cardiomyopathy model (TAC surgery) in SCOT-Heart-KO mice that lack the key enzyme needed for ketone oxidation show a marked rise in cardiac ROS, and by eight weeks they develop significant left ventricular dilation, reduced ejection fraction, and more severe adverse ventricular remodeling [15]. Furthermore, diminished ketone body metabolism exacerbates oxidative stress. Ketone oxidation

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reduces ROS by sustaining a high NAD^+/NADH ratio and oxidizing ubiquinone. When metabolism is insufficient, this protection is lost, increasing oxidative damage to cardiac proteins. For example, SCOT-Heart-KO mice showed a doubling of carbonylated proteins in the heart four weeks post-TAC surgery, indicating increased oxidative stress-related injury [15].In addition, ketone metabolism is closely linked to myocardial protein acetylation, and reduced metabolic rates lower overall acetylation levels [15]. In SCOT-Heart-KO mice, acetylated lysine residues are decreased. Since acetylation is essential for proteins involved in fatty acid oxidation, the TCA cycle, and the electron transport chain, such changes may further worsen cardiac dysfunction.

Studies show that a ketogenic diet significantly increases the level of βOHB in the hearts of spontaneous hypertensive rats (SHRs), which worsens cardiac interstitial fibrosis [16]. In cell experiments, when βOHB acts with transforming growth factor-β (TGF-β), it activates the mTORC2 pathway and significantly increases the expression of collagen 1 and collagen 3 in cardiac fibroblasts. These two collagens are key markers of myocardial fibrosis.

Furthermore,research has found that when ketone levels rise far above normal pathological ranges (for example, much higher than 600 μM), they may compete with other substrates such as glucose or fatty acids and suppress their oxidation [17]. This disruption can disturb the failing heart's metabolic balance and reduce the stability of the energy supply.

5. Potential therapeutic role of ketones in the heart

5.1. Treatable symptoms

Pathological ventricular remodeling symptoms: In a TAC surgery, SCOT-Heart-KO mice showed marked increases in left ventricular volume, reduced ejection fraction and thinner relative wall thickness [15]. Normal ketone metabolism in control mice preserved heart structure and function, suggesting a protective role against pathological remodeling-induced cardiac enlargement and systolic dysfunction.

Following pressure overload, impaired cardiac ketone metabolism elevates ROS, resulting in oxidative stress-related symptoms [15]. On the other hand, AcAc can markedly lower mitochondrial superoxide production. By helping maintain redox balance, ketone oxidation may reduce oxidative stress injury and protect the heart from structural damage and functional decline.

5.2. Therapeutic approaches

One feasible treatment method is to raise blood ketone levels through diet, such as using a ketogenic diet, which provides high fat, very low carbohydrate [15]. Ketogenic diets in wild-type mice significantly elevate serum ketones without impairing cardiac function, suggesting enhanced cardiac energy metabolism via circulating ketones. This may reduce reliance on fatty acid oxidation and oxidative stress during heart injury.

Another possible treatment is to protect or increase the activity and expression of SCOT [15]. SCOT, the terminal enzyme in ketone body oxidation, is critical; its deficiency in cardiomyocytes exacerbates cardiac remodeling and oxidative stress post-pressure overload. Thus, therapeutic agents enhancing SCOT expression or activity could sustain cardiac ketone oxidation, preserve redox balance, and bolster heart function during injury.

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6. Conclusion

This review examines how ketone body metabolism affects mitochondrial function in cardiomyocytes and cardiomyopathy. It explores ketone metabolism, mitochondrial functions, and cardiomyopathy's causes and symptoms. Excessive ketone accumulation impairs mitochondrial function by lowering intracellular pH, potentially causing ketosis or ketoacidosis. Excessive ketone oxidation depletes NAD^+, disrupting energy metabolism, while insufficient ketone production leads to acetyl-CoA accumulation, abnormal protein acetylation, and obstructed energy metabolism. Low cardiac ketone metabolism exacerbates pathological remodeling by increasing ROS production, impairing mitochondrial and myofibril structure, and reducing protein acetylation, worsening cardiac dysfunction. Conversely, excessive ketone elevation may drive myocardial fibrosis by activating the mTORC2 pathway and disturbing energy balance.

These data indicate that imbalanced ketone metabolism impairs mitochondrial function and cardiac homeostasis, underscoring the need for optimized metabolic control for cardioprotection. Ex vivo heart models have inherent limitations in replicating physiological conditions. Cardiac catheterization blood samples offer a valuable approach. Further research into pharmacological or dietary modulation of ketone body metabolism is crucial. Safe, controlled ketone body interventions may improve cardiovascular health and longevity.

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