Cell Metabolism
Previews

Ketones regulate endothelial homeostasis

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In a recent paper in *EMBO Molecular Medicine*, Weis et al. reveal that cardiac endothelial cells can oxidize ketone bodies, which enhances cell proliferation, migration, and vessel sprouting. Furthermore, increasing ketone body levels with a ketogenic diet can increase endothelial cell proliferation and prevent blood vessel rarefication in hypertrophied mouse hearts. This suggests that increasing endothelial cell ketone oxidation has potential in treating heart failure.

Considerable recent interest has focused on the role of ketones in the setting of heart failure. Increased ketone oxidation rates may be an adaptive process that increases energy production to the energy-starved failing heart (Horton et al., 2019). An increased supply of ketones to the heart may also partially explain the profound benefit that SGLT2 inhibitors have in heart failure patients (Verma et al., 2018). In a provocative study by Weis et al. (2022), ketone oxidation in cardiac endothelial cells (ECs) prevented blood vessel rarefication in failing hearts. In particular, increasing ketone oxidation in cardiac ECs resulted in increased EC proliferation, migration, and vessel sprouting (Weis et al., 2022). This potential role of ketone oxidation in promoting EC proliferation is intriguing, but also confusing, as increases in mitochondrial oxidative metabolism are usually associated with decreases in the proliferative potential of cells.

Proliferating cells such as cancer cells, or hematopoietic stem/progenitor cells, are associated with high glycolytic rates and low mitochondrial oxidative rates. Indeed, high aerobic glycolysis and subsequently lowered mitochondrial oxidation of the pyruvate generated from glycolysis (i.e., the Warburg effect) is a hallmark of rapidly proliferating cells. In ECs, stimulating glycolysis promotes vessel sprouting and angiogenesis, while inhibiting glycolysis decreases EC sprouting and vessel formation (Figure 1) (De Bock et al., 2013). Conversely, inhibiting mitochondrial respiration is also associated with an increased proliferation potential of ECs and other cell types. Because proliferating cells have a high energy requirement, why should stimulating ketone oxidation increase EC proliferation? In the Weis et al. study, it is suggested that ketone body oxidation in ECs fuels energy as well as biomass production, which facilitates the increased proliferation, migration, and sprouting potential. The question arises, however, as to what effect increased ketone oxidation has on glycolysis in these cardiac ECs. In cardiomyocytes, it is generally accepted that increased ketone oxidation decreases glycolysis (Russell et al., 1997; Verma et al., 2018). Whether ketones decrease or increase EC glycolytic rates has yet to be answered and should be investigated in future studies.

While increasing ketone body levels with a ketogenic diet was shown by Weis et al. to increase cardiac EC proliferation, this effect was not observed in ECs from skeletal muscle, brain, liver, and lung. Other studies have suggested a key role for ketones and a ketogenic diet in decreasing tumor cell proliferation (Ferrere et al., 2021; Singh et al., 2015). Indeed, the main ketone in humans, β-hydroxybutyrate (βOHB), has anti-tumor properties (Ferrere et al., 2021). The ketogenic diet has also been shown to decrease tumor proliferation by decreasing rates of glycolysis (Singh et al., 2015). A potential mechanism for this is through the inactivation of the insulin/IGF-1-dependent phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway and the activation of AMPK, as well as through increased mitochondrial enzymes and protein content, along with increased fatty acid oxidation.

βOHB is not only a fuel source, but also has cell signaling properties, including the inhibition of histone deacetylases (HDACs) (Figure 1) (Jurkin et al., 2011; Mierziak et al., 2021) and the capacity to increase differentiation and reduce proliferation of cancerous cells (Jurkin et al., 2011). HDACs alter gene expression through the regulation of chromatin structure and increase differentiation while reducing proliferation of cancerous cells (Jurkin et al., 2011). Furthermore, HDAC2 knockdown is associated with the upregulation of cyclin-dependent kinase inhibitors, p21 and p27, which are important enzymes in the regulation of the cell cycle (Jurkin et al., 2011). βOHB specifically seems to inhibit HDAC2 by increasing histone p21 gene expression (Mierziak et al., 2021). Collectively, ketone-induced stimulation of EC proliferation seems to be restricted to cardiac tissue and further mechanistic studies are warranted to determine why cardiac ECs demonstrate a polarized response to ketone oxidation.

Ketone body supplementation can enhance respiratory efficiency of cardiomyocytes in the failing heart, decrease inflammation, and prevent micro-vessel rarefication (Horton et al., 2019; Weis et al., 2022). Vascular rarefaction is a characteristic sign of pathological cardiac hypertrophy associated with maladaptive cardiac remodeling and dysfunction (Nakamura and Sadoshima, 2018). The question arises as to the best way to provide supplemental ketone bodies. Ketone infusions can improve heart function in patients with heart failure but are impractical for long-term use. The ketogenic diet also increases

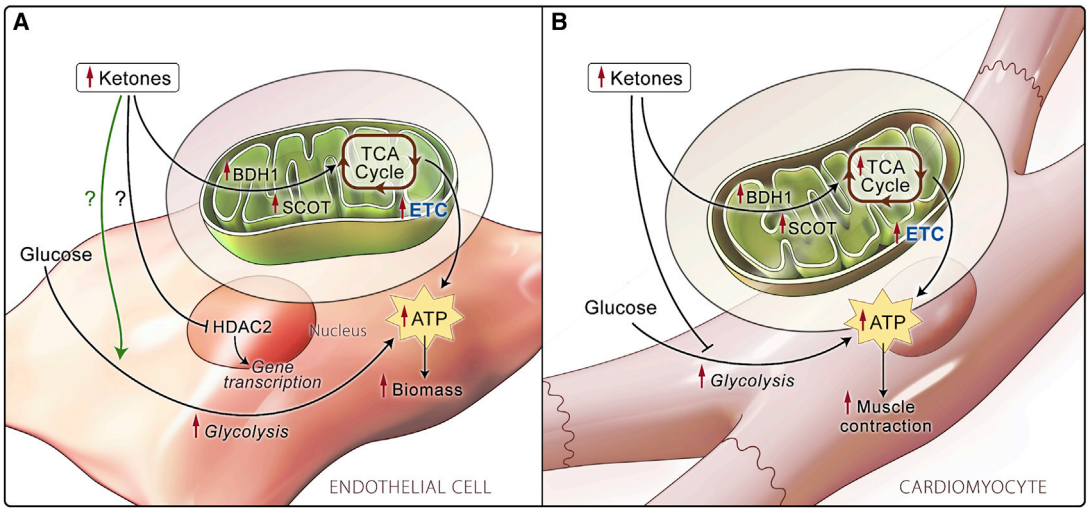

Figure 1. Effects of increasing ketones on endothelial cells and cardiomyocytes in the failing heart
In both endothelial cells (A) and cardiomyocytes (B), increasing ketone levels increases tricarboxylic acid (TCA) cycle activity and ATP production, which may increase biomass production in endothelial cells and contraction of cardiomyocytes. Glycolysis can also increase biomass production and proliferation in endothelial cells, but the effects of ketones on glycolysis are not clear. Ketones also have the potential to inhibit HDAC2, but whether this occurs in endothelial cells leading to decreased gene transcription is not clear.

circulating ketone levels but raises circulating fatty acid levels that can have a negative impact on heart failure. Use of SGLT2 inhibitors also increases circulating ketone levels (Al Jobori et al., 2017), but while they have marked beneficial effects in heart failure, their effects on EC proliferation have yet to be explored. Ketone ester drinks are now being investigated as an approach to treat heart failure, although their impact on EC proliferation has not yet been established.

Excess inflammation is a hallmark of atherosclerotic plaque formation and EC dysfunction during diabetes. During atherosclerosis, activated monocytes adhere to the damaged endothelium and extravasate through the endothelial layer and secrete inflammatory cytokines, which stimulate inflammatory macrophage differentiation and lipid-laden foam cell formation. High ketone levels increase NOX-4 isoform expression, leading to increased reactive oxygen species (ROS) in ECs. In turn, increased ROS leads to endothelial intercellular adhesion molecule-1 (ICAM-1) overexpression, and subsequent monocyte adhesion and MCP-1 and IL-8 secretion, which exacerbates the inflammatory state (Kanikarla-Marie and Jain, 2015). Although severe hyperketonemia (5–10 mmol/L) is positively associated with increased inflammation and atherosclerotic plaque progression, the findings in Weis et al. highlight that concentration- and tissue-specific effects of ketone exposure can provocatively enhance EC proliferation, migration, and sprout formation, which would instead predict cardioprotection. Thus, further studies are warranted in models of atherosclerosis and diabetes to determine whether ketone exposure can mediate beneficial vascular remodeling.

DECLARATION OF INTERESTS

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