Redox Biology 18 (2018) 25–32

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Research paper

Adropin regulates pyruvate dehydrogenase in cardiac cells via a novel GPCR-MAPK-PDK4 signaling pathway

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ARTICLE INFO

Keywords:
Adropin
Mitochondria
PDK4
GRP19
GPCR
Pyruvate dehydrogenase
Metabolism

ABSTRACT

Mitochondria supply ~90% of the ATP required for contractile function in cardiac cells. While adult cardiomyocytes preferentially utilize fatty acids as a fuel source for oxidative phosphorylation, cardiac mitochondria can switch to other substrates when required. This change is driven in part by a combination of extracellular and intracellular signal transduction pathways that alter mitochondrial gene expression and enzymatic activity. The mechanisms by which extracellular metabolic information is conveyed to cardiac mitochondria are not currently well defined. Recent work has shown that adropin – a liver-secreted peptide hormone – can induce changes in mitochondrial fuel substrate utilization in skeletal muscle, leading to increased glucose use. In this study, we examined whether adropin could regulate mitochondrial glucose utilization pathways in cardiac cells. We show that stimulation of cultured cardiac cells with adropin leads to decreased expression of the pyruvate dehydrogenase (PDH) negative regulator PDK4, which reduces inhibitory PDH phosphorylation. The downregulation of PDK4 expression by adropin is lost when GPR19 – a putative adropin receptor – is genetically depleted in H9c2 cells. Loss of GRP19 expression alone increased PDK4 expression, leading to a reduction in mitochondrial respiration. Finally, we show that adropin-mediated GPR19 signaling relies on the p44/42 MAPK pathway, and that pharmacological disruption of this pathway blocks the effects of adropin on PDK4 in cardiac cells. These findings suggest that adropin may be a key regulator of fuel substrate utilization in the heart, and implicates an orphan G-protein coupled receptor in a novel signaling pathway controlling mitochondrial fuel metabolism.

1. Introduction

Cardiac mitochondria supply ~90% of the energy required for contractile function via oxidative phosphorylation (reviewed in [10]). Under non-ischemic conditions in healthy individuals, most of this ATP production occurs through the fatty acid oxidation (FAO), with the remainder coming from other sources such as glucose and ketones [10]. While hearts have a clear preference for fatty acids under normal conditions, they must maintain a level of fuel substrate flexibility to provide efficient cardiac function under stress. This is exemplified by cardiac disease states such as diabetic cardiomyopathy, where increased plasma fatty acid levels and decreased glucose uptake lead to an over-reliance on FAO for energy production. This can lead to a decrease in cardiac energy efficiency, which can exacerbate the bioenergetic deficits that characterize these disease states [2].

To address the metabolic dysfunction in cardiovascular diseases, research has focused on the pharmacological inhibition of cardiomyocyte FAO to promote the oxidation of glucose (a more efficient fuel in terms of ATP per mole of O_2 used). These studies have led to the development of several drugs (e.g. etomoxir, perhexiline) that show great therapeutic potential, but have had limited clinical success due to off-target effects [7]. As such, novel strategies to promote a switch from fatty acid to glucose oxidation in the heart have been heavily investigated. In 2008, Butler and colleagues identified a novel liver-secreted peptide hormone called adropin, which was shown to reduce insulin resistance and hepatosteatosis in mice subject to diet-induced obesity [9]. Adropin has subsequently been shown to regulate endothelial function via upregulation of eNOS expression [11], and may

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https://doi.org/10.1016/j.redox.2018.06.003
Received 14 May 2018; Received in revised form 6 June 2018; Accepted 8 June 2018
Available online 09 June 2018
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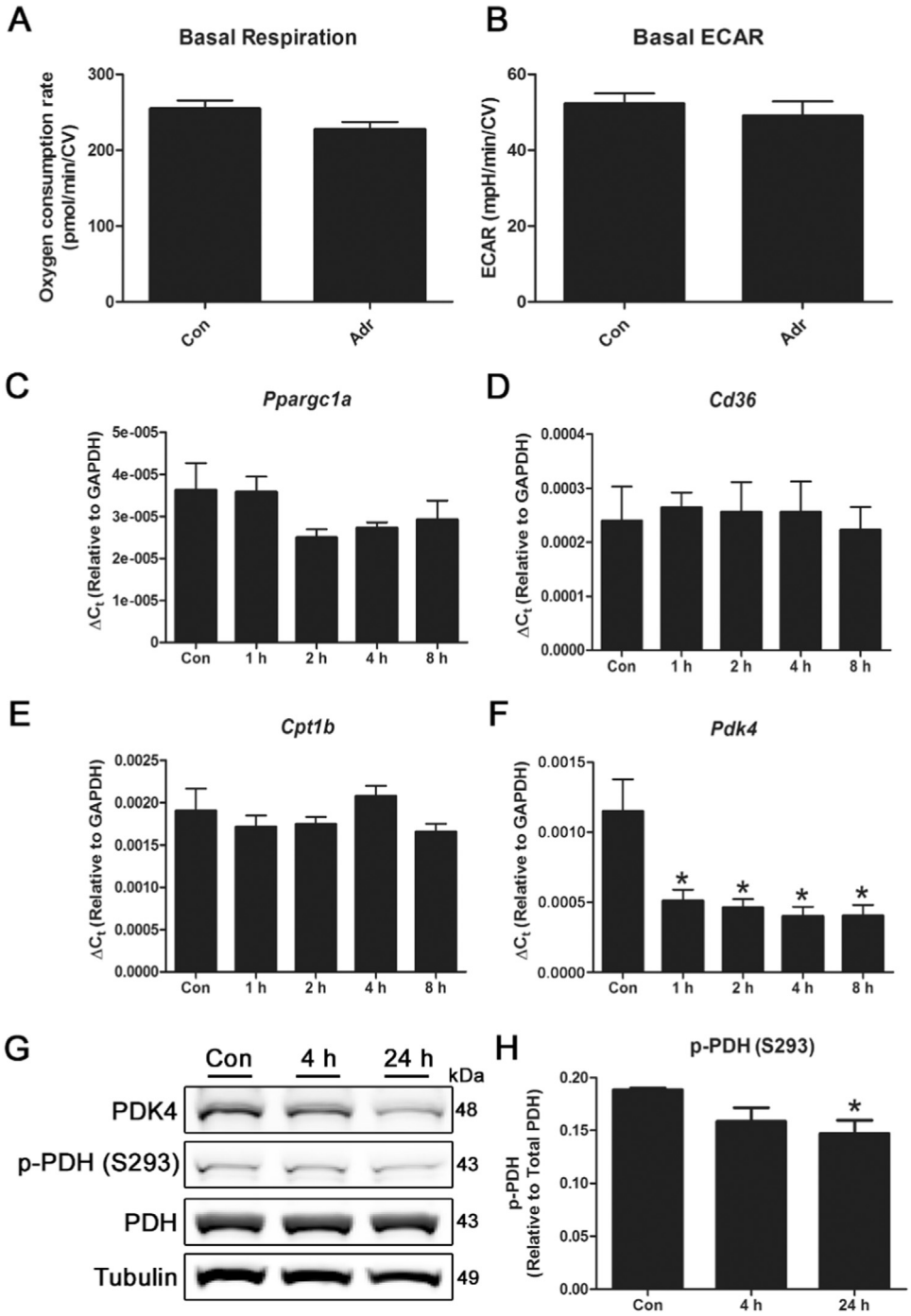

Fig. 1. Treatment of cardiac cells with adropin reduces PDK4 expression and PDH phosphorylation. Treatment of H9c2 cardiac cells with 0.5 μg/mL adropin for 4 h does not have a significant effect on basal respiration or glycolysis in Seahorse XF assays (A-B). N = 12. Exposure of cells to adropin for 0–8 h leads to a reduction in *Pdk4* expression, while levels of *Ppargc1a, Cd36* and *Cpt1b* remain unchanged (C-F). The reduction in PDK4 protein abundance results in a decrease in PDH phosphorylation at serine 293 after 24 h (G-H). N = 3–4. * = $P < 0.05$.

contribute to decreased arterial stiffness [3]. Importantly, recent work has shown that in skeletal muscle, adropin could promote the use of glucose as an oxidation substrate in obese animals, by downregulating the cellular FAO machinery and promoting glucose uptake into myocytes [4,5]. This led to improvements in insulin sensitivity and glucose tolerance in obese mice, indicating strong effects on metabolism at the cellular and systemic level [4,5].

The switch to glucose utilization from FAO in skeletal muscle seen in adropin-treated animals led us to investigate whether this peptide would have the same effect in cardiac cells. Using cultured cardiac cells, we show that adropin downregulates the expression of the mitochondrial pyruvate dehydrogenase (PDH) kinase, PDK4, leading to a decrease in inhibitory PDH phosphorylation. We then investigated the mechanism behind adropin signaling in cardiac cells, and show that the orphan GPCR protein GPR19 acts as the receptor for this peptide hormone. Genetic depletion of GPR19, or blocking its downstream signaling via p44/42 MAP kinases, prevents the action of adropin on PDK4 in cardiac cells. In summary, we show that adropin is a potential tool for future studies into the regulation of mitochondrial energy metabolism in the heart.

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