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THE ROLE OF β-ARRESTIN PROTEINS IN CARDIAC ENERGY METABOLISM

KARDİYAK ENERJİ METABOLİZMASINDA β-ARRESTİN PROTEİNLERİNİN ROLÜ

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ABSTRACT

Objective: *β-arrestins are G-protein coupled receptor (GPCR) signal regulation proteins. These proteins are involved in metabolic or functional effects of agonist and biased agonist ligands. The aim of this study was to evaluate the potential effects of β-arrestins on cardiac substrate metabolism.*
Material and Method: *To eliminate G-protein effects and to focus specifically on the β-arrestin signal, we used carvedilol, a β-arrestin-biased agonist. Changes in glucose and palmitate oxidation after carvedilol administration were assessed in control mouse hearts. Western blotting was used to evaluate the phosphorylation levels of protein kinase B (Akt), extracellular signal-regulated kinase (ERK) and pyruvate dehydrogenase (PDH) proteins in these hearts. Hypertrophy was induced with phenylephrine in H9c2 cells. Glucose metabolism was measured in cells treated with carvedilol or prazosin using insulinated perfusate.*
Result and Discussion: *Carvedilol did not alter glucose or palmitate oxidation rates in control mouse hearts. However acute administration of carvedilol influenced ERK and PDH phosphorylation in the hearts. In hypertrophied H9c2 cells, carvedilol treatment decreased glycolysis and slightly increased glucose oxidation which resulted in a significant amelioration in glycolysis-glucose oxidation coupling. In conclusion, carvedilol and β-arrestins may improve glucose metabolism.*
Keywords: *β-arrestin, carvedilol, glycolysis, glucose oxidation, palmitate oxidation*

ÖZ

Amaç: *β-arrestinler G-proteini ile kenetli reseptörlerin (GPKR) sinyallerini düzenleyen proteinlerdir. Bu proteinler, agonist ve bias agonist ligandların metabolic ve fonksiyonel etkilerine aracılık ederler. Bu çalışmada, β-arrestinlerin kardiyak substrat metabolizması üzerindeki potansiyel etkilerinin değerlendirilmesi amaçlanmıştır.*
Gereç ve Yöntem: *G-proteinlerinin etkisini ortadan kaldırmak ve sadece β-arrestin sinyaline odaklanabilmek için bir β-arrestin-bias agonist olan karvedilol kullanılmıştır. Kontrol fare kalplerinde karvedilol uygulaması sonrası glukoz ve palmitat oksidasyonundaki değişiklikler değerlendirilmiştir. Protein kinaz B (Akt), ekstrasellüler sinyal düzenleyici kinaz (ERK) ve pirüvat dehidrogenaz (PDH) fosforilasyonları Western blot yöntemi ile değerlendirilmiştir. Ayrıca H9c2 hücre hattında fenilefrin ile hipertrofi oluşturulmuş; karvedilol veya prazosin-tedavili hücrelerde glukoz metabolizması değerlendirilmiştir.*

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Sonuç ve Tartışma: *Karvedilol kontrol fare kalplerinde glukoz ve palmitat oksidasyonunu etkilememiştir. Öte yandan akut karvedilol uygulaması bu kalplerde ERK ve PDH fosforilasyonlarını değiştirmiştir. Hipertrofik H9c2 hücrelerde karvedilol tedavisi glikolizi azaltmış ve glukoz oksidasyonunu artırmıştır. Bu durum hipertrofide bozulmuş olan glikoliz-glukoz oksidasyonu kenetlenmesinde düzelmeye aracılık etmiştir. Sonuç olarak karvedilol ve β-arrestin proteinlerinin glukoz metabolizmasını iyileştirebileceği sonucuna ulaşılmıştır.*
Anahtar Kelimeler: *β-arrestin, glikoliz, glukoz oksidasyonu, karvedilol, palmitat oksidasyonu*

INTRODUCTION

β-arrestins are intracellular signalling proteins that have a pivotal role in regulating the function of G-protein coupled receptors (GPCRs). They are initially recognized as adaptors that uncouple and inactivate the GPCRs that they interact with. Upon agonist stimulation, GPCR signalling is terminated by phosphorylation by GPCR kinases (GRKs), which increase the affinity of each receptor for *β*-arrestin [1,2]. Recent studies have revealed new insights about the interaction between *β*-arrestins and activated GPCRs. According to these insights, biased ligands of GPCR that activate either G-protein or *β*-arrestin-mediated signalling hold a big therapeutic potential. The signalling processes regulated by *β*-arrestin proteins are not fully understood. However, recent data have shown a close relation between *β*-arrestin deficiency and metabolic or cardiovascular diseases [3-5].

As a *β*-adrenergic receptor agonist (*β*-AR), isoprenaline stimulates both G-protein and *β*-arrestin. Chronic exposure to isoprenaline leads to GRK-mediated β-arrestin 2 activation and recruitment at *β*1-AR and *β*2-AR, which causes receptor desensitization [6]. Isoprenaline exposure, which has also been used as a cardiac dysfunction model in rodents [7], affects not only the haemodynamic structure of the heart but also its metabolic function. Isoprenaline perfusion increases both glycolysis and glucose oxidation in rat hearts [8]. As downstream proteins, β-arrestin proteins could be involved in the metabolic impacts of isoprenaline.

Carvedilol, a non-selective *β* and selective *α*1-receptor antagonist [9], is utilized for the treatment or prevention of certain cardiovascular diseases. It has been shown to be a *β*-arrestin-biased agonist, activating *β*-arrestin signalling and blocking the deleterious effects of chronic Gs-mediated cyclic adenosine monophosphate (cAMP) signalling [10]. It triggers extracellular signal-regulated kinase (ERK) through *β*-arrestin proteins. In this study, we investigated whether *β*-arrestins are involved in cardiac energy substrate metabolism. We used carvedilol as a *β*-arrestin-biased agonist to eliminate possible G-protein effects and to focus specifically on the *β*-arrestin signal. To this end, the acute effects of carvedilol on palmitate oxidation and glucose oxidation rates were assessed in heart tissues. Since chronic insulin stimulation downregulates the *β*-arrestin 1 signal [11], we also investigated the effect of carvedilol on glucose utilization in hypertrophied H9c2 cells in the presence of insulin.

MATERIAL AND METHOD

Animals

All operations were sanctioned by the Health Sciences Animal Policy and Welfare Committee of University of Alberta (AUP-288). The Canadian Council on Animal Care guidelines have been followed for care. Eight-week old C57Bl/6J male mice were maintained at the Health Sciences Lab Animal Services facility in University of Alberta. 12 h light/dark cycle applied during maintenance with constant temperature/ humidity.

Isolated Working Mice Hearts

The acute effect of carvedilol administration on fatty acid (palmitate) oxidation and glucose oxidation rates were measured with isolated working heart preparations. Initially, mice were anesthetized using i.p sodium pentobarbital injection (60 mg/kg). Cardiac tissues were subsequently isolated and perfused for 60 min with Krebs–Henseleit buffer with 0.8 mM palmitate (Sigma-Aldrich) pre-bound to 3% bovine serum albumin (BSA, Equitech-Bio, Inc.) and 5 mM glucose. All hearts were perfused with vehicle (H2O: dimethyl sulfoxide, 40:60) for 30 min and 1 μM carvedilol was then

administered to the perfusion buffer for the last 30 min. In the final perfusate, the amount of DMSO was diluted to a negligible level (~10^5x).

Palmitate and glucose oxidation rates were evaluated by the quantitative collection of ^3H_2O produced from [9,10-^{3}H] palmitate and $^{14}CO_2$, from [U-^{14}C] glucose, respectively. ATP production rates were calculated by multiplying the rates of glucose and fatty acid oxidation and the number of ATP molecules produced from these processed (31 and 105, respectively). The outcomes were transformed into percentages to evaluate the contribution of these oxidation processes to the overall cardiac ATP production.

Hearts were rapidly frozen in liquid nitrogen after the procedure and kept at -80°C for Western blot analysis.

Cell Culture

H9c2 cells (ATCC, VA, USA), originating from rat heart, were cultured in Dulbecco's Modified Eagles Medium (DMEM, Sigma, Germany) with 10% (v/v) FBS and 1% (w/v) penicillin-streptomycin (Sigma). Trypsinization was carried out for once the cells reached 70-80% confluency. Cardiac cell differentiation was induced with a medium with 1% FBS and 1 μM retinoic acid (RA, Sigma) for 7 days. Differentiation was confirmed through morphological characteristics on light microscopy.

The cells were incubated with phenylephrine (PE, catalog P6126, Sigma, 1 μM) to induce hypertrophy and treated with carvedilol (catalog sc-200157, Santa Cruz, 1 μM) or prazosin (catalog p7791, Sigma, 1 μM) during the last four days of differentiation. Experimental groups were as follows:

C: Control
H: PE-Hypertrophy
CC: Control + Carvedilol
CP: Control + Prazosin
HC: PE-Hypertrophy + Carvedilol
HP: PE-Hypertrophy + Prazosin

Cell Perfusions

By the end of 7 days, cells were perfused for metabolic measurements. The perfusion solution was Krebs Henseleit buffer containing palmitate (0.8 mM) bound to 4% fatty acid free BSA, glucose (5 mM), and insulin (100 μU/ml; HumulinR). Glucose in the buffer was radiolabeled with [5-3H] glucose and [U-14C]-glucose to specifically measure the amounts of $3H_2O$ (for glycolysis) and $14CO_2$ (for glucose oxidation).

Proton production was determined by taking the glycolysis rate and subtracting the glucose oxidation rate, then multiplying the resulting difference by two [12].

Western Blots

Cells or frozen tissues were homogenized in a lysis buffer (RIPA). To detect protein concentration, Bradford protein assay was used. Lysates containing same amount of protein (20 μg) were loaded into sodium dodecyl sulfate polyacrylamide gel and separated by electrophoretic principle. At 22V during overnight, proteins were transferred to a nitrocellulose membrane. Membranes were then blocked at room temperature for 1 h in tris buffered saline with Tween 20 (0.1%) (TBS-T) and milk powder (5%) to avoid non-specific binding. Subsequently, membranes were kept in the primary antibodies [phospho- protein kinase B (Akt) (CST, #9271S), Akt (CST #9272S), phosphorylated pyruvate dehydrogenase (phospho-PDH) (CST, #31866), PDH (CST, #2784), phospho-ERK (CST, #9101), ERK (CST, #9102)] overnight at + 4°C. After washing processes with TBS-T, membranes were incubated for 1 h with corresponding secondary antibodies (CST, #7074) at room temperature. After two min enhanced chemiluminescence incubation, chemiluminescent signals were reflected on X-ray film. Signal quantification was analysed with Image J®.

Statistical Analysis

Data are expressed as the mean ± SEM. Student's t-test or One-Way ANOVA followed by a Tukey post hoc test was performed to determine significant differences which were considered

significant when $p<0.05$. Statistical analysis was carried out using the GraphPad Prism V9 statistics software. The figures show the exact p-values.

RESULT AND DISCUSSION

Acute Carvedilol Effects on Glucose Oxidation and Palmitate Oxidation Rates

Cardiac function parameters were obtained during perfusion of the hearts with vehicle for 30-min and then with carvedilol for 30-min. There was no significant difference between these functional parameters in the presence or absence of carvedilol (Table 1).

Table 1. Acute carvedilol effects on ex vivo measures of cardiac function in isolated working mice hearts. After 30-min perfusion with vehicle, carvedilol (1μM) was administered to perfusion buffer. The means of the first 30-min and last 30-min were compared (n=12).

Cardiac Function Parameters	Perfusion with Vehicle for 30 min	Perfusion with Carvedilol for 30 min
Heart Rate (HR) (b.p.m.)	330.80±33.44	331.90±35.90
Peak Systolic Pressure (PSP) (mmHg)	71.33±1.13	71.08±0.93
Developed Pressure (DP) (mmHg)	23.33±1.32	21.50±1.21
HR x PSP (b.p.m. • mmHg • 10^{-3})	23.50±2.31	23.75±2.64
HR x DP (b.p.m. • mmHg • 10^{-3})	23.33±1.32	21.50±1.21
Cardiac Output (mL • min^{-1})	9.70±0.79	8.33±1.02
Aortic Outflow (mL • min^{-1})	6.82±0.57	5.91±0.85
Coronary Flow (mL • min^{-1})	2.88±0.33	2.94±0.36
Cardiac Work (joules • min^{-1} • g dry wt^{-1})	2.24±0.20	2.03±0.6
Cardiac Work (mmHg • ml^{-1} • min^{-1})	6.92±0.56	6.30±0.74

Cardiac work was used to normalize cardiac oxidation rates. There was no significant alteration in either cardiac glucose oxidation rates (Figure 1A) or normalized glucose oxidation rates (Figure 1B) with the acute carvedilol administration. Acute carvedilol administration had no effect on the palmitate oxidation rates and normalized palmitate oxidation rates (Figure 1C and 1D). As expected, ATP production rates from fatty acid and glucose oxidation were not altered by carvedilol (data not shown).

Protein Levels of ERK, Akt and PDH

ERK phosphorylation was evaluated as an indicator of biased agonist property of carvedilol. Acute administration of carvedilol triggered ERK phosphorylation (Figure 2A). To assess insulin sensitizing effects of carvedilol, phospho-Akt expression was also examined. Carvedilol did not change the levels of phospho-Akt (Figure 2B). Interestingly, carvedilol stimulated the activation of pyruvate dehydrogenase (PDH), as shown by a decrease in its phosphorylation (Figure 2C), although no significant changes occurred in glucose oxidation in the isolated working heart perfusion system.

The Metabolic Effects of Carvedilol on Control and Hypertropied H9c2 Cells: Comparison with Prazosin

To evaluate the contribution of α-blocking property of the drug to the metabolic effects, we compared the direct metabolic effects of carvedilol with the selective α1-blocker prazosin in cells. Cell size was measured to confirm the development of hypertrophy induced by PE (Figure 3A). Carvedilol or prazosin was added to the media on the fourth day of PE incubation (Figure 3B). Both carvedilol and prazosin lowered the cell size of the hypertrophied cells (Figure 3C).

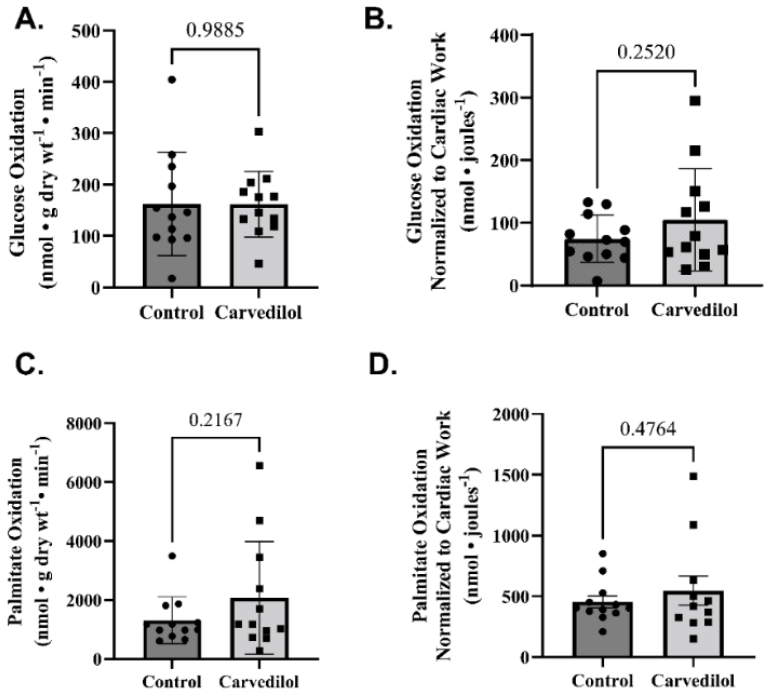


Figure 1. The acute effects of carvedilol on substrate metabolism. Isolated working heart glucose oxidation rates (A), glucose oxidation rates normalized to cardiac work (B), palmitate oxidation rates (C) and palmitate oxidation rates normalized to cardiac work (D) (n=12)

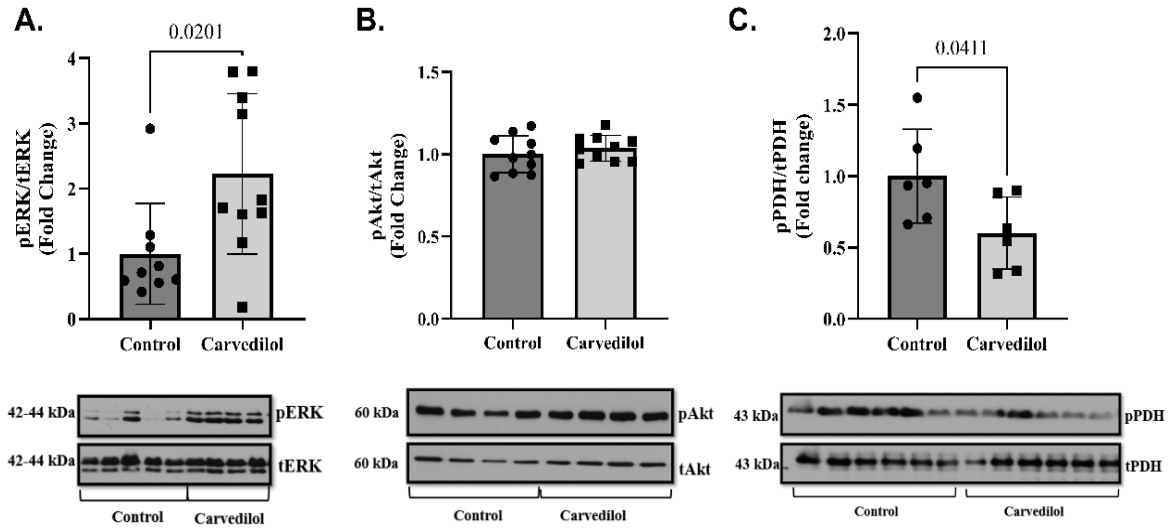


Figure 2. Carvedilol effects on some protein phosphorylations. Phosphorylation levels of ERK (A), Akt (B) and PDH (C). Values normalized to total levels of corresponding protein (n=6-10)

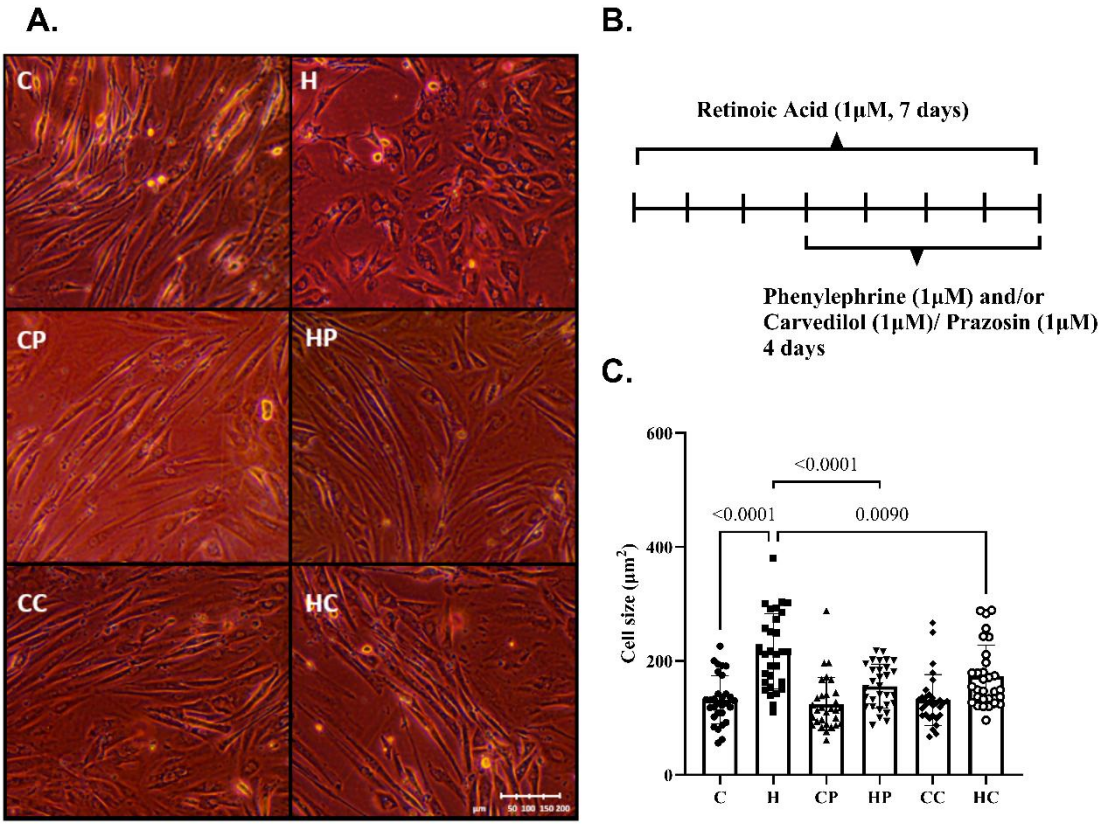


Figure 3. Carvedilol effects on cell size in H9c2 cells treated with phenylephrine. Representative images (A), treatment protocol (B), cell size measurement (n=30 cells) (C), of control and H9c2 cells (C: Control H: Hypertrophied, CP: Control+Prazosin, HP: Hypertrophy+Prazosin, CC: Control+Carvedilol, HC: Hypertrophy+Carvedilol)

There was a slight but not significant rise in glycolysis in hypertrophied cells. Carvedilol prevented this increase (Figure 4A). Glucose oxidation was similar in all groups (Figure 4B). However, a mild increase in glucose oxidation in carvedilol-treated hypertrophied cells resulted in a reduction in proton production (Figure 4C). Prazosin had no effect on glucose metabolism in H9c2 cells.

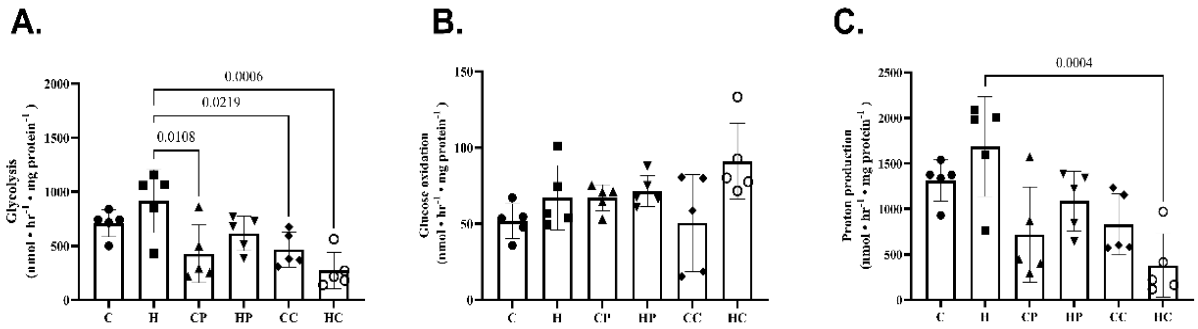


Figure 4. Carvedilol's metabolic effects in H9c2 cells. Glycolysis (A), glucose oxidation (B) and proton production rates (C) of control and H9c2 cells (C: Control H: Hypertrophied, CP: Control+Prazosin, HP: Hypertrophy+Prazosin, CC: Control+Carvedilol, HC: Hypertrophy+Carvedilol) (n=5)

To evaluate the effects of β-arrestin proteins on cardiac energy metabolism we used carvedilol due to its β-arrestin biased agonist property. First, the impact of carvedilol on glucose oxidation and fatty acid oxidation rates, two important components of cardiac energy substrate metabolism, was evaluated acutely in control mouse hearts. Carvedilol did not affect cardiac function or glucose and fatty acid oxidation rates in isolated working mouse hearts. In a previous study, carvedilol was shown to diminish palmitate oxidation and increase glycolysis in C2C12 cell lines [13]. In another study, increased CD36 expression, which is responsible for fatty acid uptake, was inhibited by carvedilol treatment in cardiac and skeletal muscle of streptozotocin (STZ)-diabetic rats [14]. In the current study, carvedilol decreased PDH phosphorylation. This modification would be expected to cause to an increase in mitochondrial glucose oxidation, since PDH activity -in its dephosphorylated state- modulates the transformation of pyruvate to acetyl-CoA for oxidation [15]. A similar phenomenon, acute activation of PDH increasing glucose oxidation in muscle without any alteration in glucose uptake, was reported by Small et al., where the authors concluded that under insulin-stimulated conditions PDH activity is not the only determinant of glucose uptake into mitochondria [16]. In the absence of insulin in the perfusate, carvedilol still might have stimulated PDH activation, but did not result in a measurable increase in glucose oxidation rates in our study.

It has been shown that, among other β-blockers, only carvedilol does not decrease cardiomyocyte contractility, but in fact improves it [17]. In our former study, we showed that carvedilol improved the functional deterioration of the STZ-diabetic rat heart [14]. This improvement was accompanied by an increase in β-arrestin 2. In the present study, there was no change in energy substrate utilization with carvedilol administration in mouse hearts. One explanation for this could be that there was no functional challenge in the hearts, such as what happens in diabetic cardiomyopathy.

Recent studies have shown that the effects of carvedilol on cardiac remodelling and insulin resistance correlate with the increase of the β-arrestin 2 pathway [18,19]. In these studies, carvedilol reversed the reduction in Akt phosphorylation in insulin-resistant mice. This effect was accompanied by an increase in β-arrestin 2 levels. It has been suggested that the beneficial effects of carvedilol are related to β-arrestin 2 signalling [18,19]. In our study, carvedilol induced ERK phosphorylation, which is downstream of the β-arrestin 2 signalling (Figure 5), while it did not cause a change in Akt phosphorylation. The lack of a metabolic effect, which was initially puzzling considering the alterations in cells and STZ-diabetic rats, may be the consequence of the acute and insulin-free setting of the isolated working hearts in our study. In fact, our cell studies suggest that carvedilol's non-function-related effect was to support insulin action on glucose utilization.

To investigate a possible effect of carvedilol on insulin action, we performed studies on a cardiomyocyte cell model where the increase of glucose metabolism is documented in the presence of insulin. Increased glycolysis rates have previously been reported in hypertrophied cells [20]. We induced hypertrophy by PE and observed the same trend in hypertrophied H9c2 cells. Carvedilol not only decreased glycolysis in hypertrophied H9c2 cells, but also improved glycolysis-glucose oxidation coupling, as evidenced by a lower proton production by the addition of the drug. When combined with our results on isolated working hearts, one explanation for the improvement in glucose oxidation with carvedilol in H9c2 cells may be due to the presence of insulin in the cell perfusions, and suggests that carvedilol may contribute to the effects of insulin on glucose usage. However, studies have reported that insulin stimulation downregulates β-arrestin 1 [11]. In our study, there appears to be an additive interaction between carvedilol and insulin. This may be due to the fact that β-arrestin 2 is the subtype of β-arrestins that carvedilol interact with. Another possible explanation for the increase in glucose oxidation in cells as opposed to the working hearts could be the duration of the treatment. Carvedilol was administered acutely for only 30 minutes to isolated working hearts, whereas the cells were exposed to the drug for the last four days of their incubation. Longer exposure to carvedilol might have a post-translational effect on the enzymes involved in substrate metabolism.

This study has some limitations that prevent firmer conclusions. One of them is the lack of a lactate measurements in both isolated working hearts and cells after the addition of carvedilol. An alteration in lactate might have given another piece of information with regards to glycolysis-glucose oxidation coupling. The other is that an animal disease model, such as ischaemia-reperfusion, would better reveal the biased effect of carvedilol.

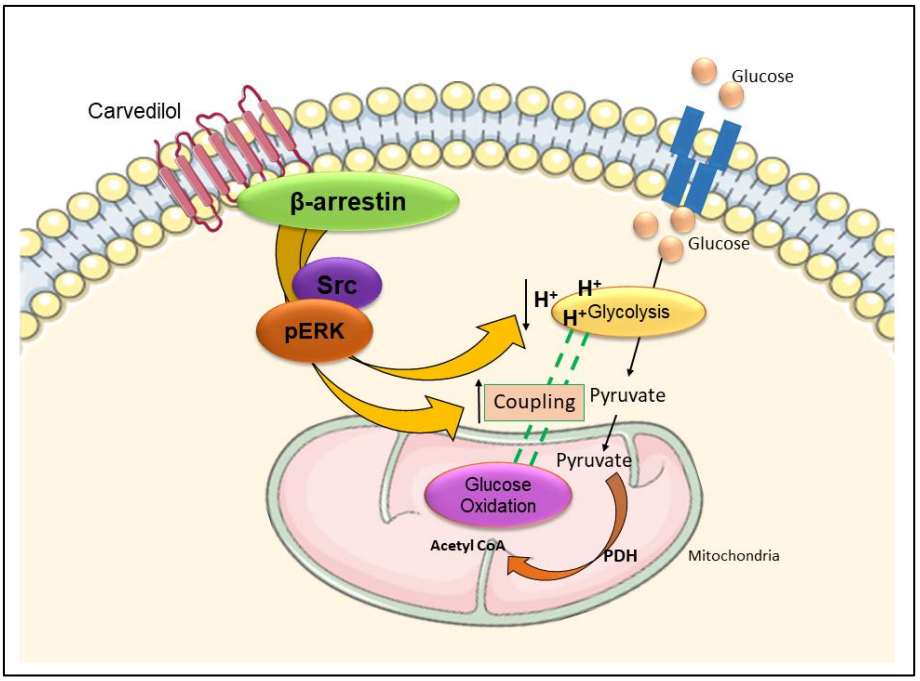


Figure 5. The effect of carvedilol and *β*-arrestins on glucose coupling

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AUTHOR CONTRIBUTIONS

Concept: B.G.C., A.O.B., G.D.L.; Design: B.G.C., K.L.P., C.S.W., Q.S., A.O.B, G.D.L.; Control: B.G.C., K.L.P., C.S.W., Q.S., A.O.B., G.D.L.; Data Collection and/or Processing: B.G.C., K.L.P., C.S.W., Q.S.; Analysis and/or Interpretation: B.G.C., A.O.B., G.D.L.; Literature Review: B.G.C., A.O.B., G.D.L.; Manuscript Writing: B.G.C., A.O.B., G.D.L.; Critical Review: B.G.C., A.O.B., G.D.L.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

All operations were sanctioned by the Health Sciences Animal Policy and Welfare Committee of University of Alberta (AUP-288). The Canadian Council on Animal Care guidelines have been followed for care.

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