The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle.


Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis.


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The pulmonary arteries (PA) in pulmonary arterial hypertension (PAH) are constricted and remodeled. They have suppressed apoptosis, partly attributable to suppression of the bone morphogenetic protein axis and selective downregulation of PA smooth muscle cell (PASMC) voltage-gated K+ channels, including Kv1.5. The Kv downregulation-induced increase in [K+]i, tonically inhibits caspases, further suppressing apoptosis. Mitochondria control apoptosis and produce activated oxygen species like H2O2, which regulate vascular tone by activating K+ channels, but their role in PAH is unknown. We show that dichloroacetate (DCA), a metabolic modulator that increases mitochondrial oxidative phosphorylation, prevents and reverses established monocrotaline-induced PAH (MCT-PAH), significantly improving mortality. Compared with MCT-PAH, DCA-treated rats (80 mg/kg per day in drinking water on day 14 after MCT, studied on day 21) have decreased pulmonary, but not systemic, vascular resistance (63% decrease, P<0.002), PA medial thickness (28% decrease, P<0.0001), and right ventricular hypertrophy (34% decrease, P<0.001). DCA is similarly effective when given at day 1 or day 21 after MCT (studied day 28) but has no effect on normal rats. DCA depletes MCT-PAH PASMC mitochondria and causes release of H2O2 and cytochrome c, inducing a 10-fold increase in apoptosis within the PA media (TUNEL and caspase 3 activity) and decreasing proliferation (proliferating-cell nuclear antigen and BrdU assays). Immunobots, immunohistochemistry, laser-captured microdissection-quantitative reverse-transcription polymerase chain reaction and patch-clamping show that DCA reverses the Kv1.5 downregulation in resistance PAs. In summary, DCA reverses PA remodeling by increasing the mitochnondria-dependent apoptosis/proliferation ratio and upregulating Kv1.5 in the media. We identify mitochondria-dependent apoptosis as a potential target for therapy and DCA as an effective and selective treatment for PAH.

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Dichloroacetate, a metabolic modulator, prevents and reverses chronic hypoxic pulmonary hypertension in rats: role of increased expression and activity of voltage-gated potassium channels.


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BACKGROUND: Chronic hypoxic pulmonary hypertension (CH-PHT) is associated with suppressed expression and function of voltage-gated K+ channels (Kv) in pulmonary artery (PA) smooth muscle cells (SMCs) and a shift in cellular redox balance toward a reduced state. We hypothesized that dichloroacetate (DCA), a metabolic modulator that can shift redox balance toward an oxidized state and increase Kv current in myoccardial cells, would reverse CH-PHT. METHODS AND RESULTS: We studied 4 groups of rats: normoxic, normoxic+DCA (DCA 70 mg. kg(-1). d(-1) PO), chronically hypoxic (CH), and CH+DCA. CH and CH+DCA rats were kept in

Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1alpha-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer.


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Pulmonary arterial hypertension (PAH) is a lethal syndrome characterized by vascular obstruction and right ventricular failure. Although the fundamental cause remains elusive, many predisposing and disease-modifying abnormalities occur, including endothelial injury/dysfunction, bone morphogenetic protein receptor-2 gene mutations, decreased expression of the O(2)-sensitive K(+)-channel (Kv1.5), transcription factor activation (hypoxia-inducible factor-1alpha (HIF-1alpha) and nuclear factor-activating T cells), de novo expression of survivin, and increased expression/activity of both serotonin transporters and platelet-derived growth factor receptors. Together, these abnormalities create a cancerlike, proliferative, apoptosis-resistant phenotype in pulmonary artery smooth muscle cells (PASMCs). A possible unifying mechanism for PAH comes from studies of fawn-hooded rats, which manifest spontaneous PAH and impaired O(2) sensing. PASMC mitochondria normally produce reactive O(2) species (ROS) in proportion to P(O2). Superoxide (PASMCs). A possible unifying mechanism for PAH comes from studies of fawn-hooded rats, which manifest spontaneous PAH and impaired O(2) sensing. PASMC mitochondria normally produce reactive O(2) species (ROS) in proportion to P(O2). Superoxide dismutase 2 (SOD2) converts intramitochondrial superoxide to diffusible H(2)O(2), which serves as a redox-signaling molecule, regulating pulmonary vascular tone and structure through effects on Kv1.5 and transcription factors. O(2) sensing is mediated by this mitochondrial-ROS-HIF-1alpha-Kv1.5 pathway. In PAH and cancer, mitochondrial metabolism and redox signaling are reversibly disordered, creating a pseudohypoxic redox state characterized by normoxic decreases in ROS, a shift from oxidative to glycolytic metabolism and HIF-1alpha activation. Three newly recognized mitochondrial abnormalities disrupt the mitochondria-ROS-HIF-1alpha-Kv1.5 pathway: 1) mitochondrial pyruvate dehydrogenase kinase activation, 2) SOD2 deficiency, and 3) fragmentation and/or hyperpolarization of the mitochondrial reticulum. The pyruvate dehydrogenase kinase inhibitor, dichloroacetate, corrects the mitochondrial abnormalities in experimental models of PAH and human cancer, causing a regression of both diseases. Mitochondrial abnormalities that disturb the ROS-HIF-1alpha-Kv1.5 O(2)-sensing pathway contribute to the pathogenesis of PAH and cancer and constitute promising therapeutic targets.

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a hypoxic chamber (10% FIO2) for 2 to 3 weeks. DCA was given either at day 1 to prevent or at day 10 to reverse CH-PHT. We used micromanometer-tipped catheters and measured hemodynamics in closed-chest rats on days 14 to 18. CH+DCA rats had significantly reduced pulmonary vascular resistance, right ventricular hypertrophy, and PA remodeling compared with the CH rats. CH inhibited I(K), eliminated the acute hypoxia-sensitive I(K), and decreased Kv2.1 channel expression. In the short term, low-dose DCA (1 microM/L) increased I(K) in CH-PASMCs. In a mammalian expression system, DCA activated Kv2.1 by a tyrosine kinase-dependent mechanism. When given long-term, DCA partially restored I(K) and Kv2.1 expression in PASMCs without altering right ventricular pyruvate dehydrogenase activity, suggesting that the beneficial effects of DCA occur by nonmetabolic mechanisms. CONCLUSIONS: DCA both prevents and reverses CH-PHT by a mechanism involving restoration of expression and function of Kv channels. DCA has previously been used in humans and may potentially be a therapeutic agent for pulmonary hypertension.

Pyruvate dehydrogenase influences post ischemic heart function.


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BACKGROUND: The pyruvate dehydrogenase (PDH) enzyme complex determines the extent of carbohydrate oxidation in the myocardium. PDH is in a largely inactive state during early reperfusion of postischemic myocardium. The resultant decrease in pyruvate oxidation in postischemic hearts has been documented with 13C nuclear magnetic resonance (NMR) spectroscopy. This study demonstrates that counteracting depressed pyruvate oxidation can enhance contractile recovery in the absence of increases in either glycolytic activity or glucose oxidation. The findings indicate that increased incorporation of carbon units from pyruvate into the intermediates of the oxidative pathways by PDH influences the metabolic efficiency and mechanical work of postischemic hearts.

METHODS AND RESULTS: Isolated rabbit hearts were situated in an NMR magnet and perfused or reperfused (10 minutes of ischemia) with 2.5 mmol/L [3-13C]pyruvate as sole substrate to target PDH directly and bypass the glycolytic pathway. Hearts were observed with or without activation of PDH with dichloroacetate. Mechanical function and oxygen consumption (MVO2) were monitored. 13C and 31P NMR spectroscopy allowed observations of pyruvate oxidation and bioenergetic state in intact, functioning hearts. Metabolite content and 13C enrichment levels were then determined with in vitro NMR spectroscopy and biochemical assay. PDH activation did not affect performance of normal hearts. Postischemic hearts with augmented pyruvate oxidation (dichloroacetate-treated) sustained improved mechanical function throughout 40 minutes of reperfusion. Rate-pressure-product (RPP) increased from 8300 +/- 1800 (mean +/- SEM) in untreated postischemic hearts to 21300 +/- 2400 in hearts treated with dichloroacetate (P < .05). Oxygen use per unit work [MVO2 multiplied by 10(4)] divided by RPP] was improved from 1.50 +/- 0.13 to 1.14 +/- 0.11 (P < .05) without differences in high-energy phosphate content between treated and untreated hearts. Values of dP/dt were also consistently higher, by as much as 185%, during reperfusion of dichloroacetate-treated, postischemic hearts during dichloroacetate treatment, reduced pyruvate oxidation from the incorporation of 13C into the tissue glutamate pool. With the tissue alanine level as a marker of 13C-enriched pyruvate availability in the cell, the ratio of labeled glutamate to alanine was only 58% of the control value during early reperfusion. With dichloroacetate, that ratio was 167% greater than that of untreated hearts (P < .05). By the end of the reperfusion period, the 13C enrichment of the tissue glutamate pool by pyruvate oxidation was elevated from dichloroacetate treatment (untreated, 62 +/- 7%; DCA-treated, 81 +/- 6%; P < .05), but glucogen content was similar in both groups and 13C enrichment of tissue alanine remained unchanged, near 60%, indicating no increases in glycolytic end product formation. CONCLUSIONS: Metabolic reversal of contractile dysfunction was achieved in isolated hearts by counteracting depressed PDH activity in the postischemic myocardium. Improved cardiac performance did not result from, nor require, increased glycolysis secondary to the activation of PDH. Rather, restoring carbon flux through PDH alone was sufficient to improve mechanical work by postischemic hearts.

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Allicin in garlic protects against coronary endothelial dysfunction and right heart hypertrophy in pulmonary hypertensive rats.


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We recently reported that coronary endothelial cell (CEC) dysfunction may contribute to the development of right ventricular (RV) hyper trophy (RVH) in monocrotaline (MCT)-induced pulmonary hypertensive rats. This present study investigated whether preservation of the coronary endothelium and its active metabolite as different garlic and its active allicin metabolite as different garlic feeding could prevent the exaggerated vasoconstrictory responses of the MCT coronary arteries. There was no change in the coronary dilatory responses to a nitric oxide donor sodium nitroprusside. Further testings of similar treatments with either boiled garlic (BG) or aged garlic (AG), which do not contain the active allicin metabolite, were ineffective. CECA function, assessed with acetylcholine-induced dilation as well as N(omega)-nitro-l-arginine methyl ester-induced constriction, revealed marked attenuation in right, but not left, coronary arteries of the MCT rats. This is consistent with our earlier report. Feeding of RG, but not BG or AG, preserved the CEC function and prevented the exaggerated vasoconstrictory responses of the MCT coronary arteries. There was no change in the coronary dilatory responses to a nitric oxide donor sodium nitroprusside. Further testings of vasodilatory activity to garlic extracts showed that only RG, but not BG or AG, elicited a potent, dose-dependent dilation on the isolated coronary. Taken together, these findings show that the protective effect of garlic against the development of RVH in MCT-treated rats is probably mediated via its active metabolite allicin action on coronary endothelial function and vasoreactivity.

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Dichloroacetate treatment partially regresses established pulmonary hypertension in mice with SM22alpha-targeted overexpression of the serotonin transporter.


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The nuclear factor of activated T cells in pulmonary arterial hypertension can be therapeutically targeted.


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In pulmonary arterial hypertension (PAH), antipapoptotic, proliferative, and inflammatory diatheses converge to create an obstructive vasculopathy. A selective down-regulation of the Kv channel Kv1.5 has been described in human and animal PAH. The resultant increase in intracellular free Ca(2+)/[Ca(2+)](i) and K(+) ([K(+)](i))) concentrations explains the pulmonary artery smooth muscle cell (PASMC) contraction, proliferation and resistance to apoptosis. The recently described PASMC hyperpolarized mitochondria and increased bcl-2 levels also contribute to apoptosis resistance in PAH. The cause of the Kv1.5, mitochondrial, and inflammatory abnormalities remains unknown. We hypothesized that these abnormalities can be explained in part by an activation of NFAT (nuclear factor of activated T cells), a Ca(2+)/calcineurin-sensitive transcription factor. We studied PASMC and lungs from six patients with and without PAH and blood from 23 PAH patients and 10 healthy volunteers. Compared with normal, PAH PASMC had decreased Kv current and Kv1.5 expression and increased [Ca(2+)](i), [K(+)](i)), mitochondrial potential (Delta Psi m), and bcl-2 levels. PAH but not normal PASMC and lungs showed activation of NFAT2. Inhibition of NFAT2 by VIVIT or cyclosporine restored Kv1.5 expression and current, decreased [Ca(2+)](i), [K(+)](i)), bcl-2, and Delta Psi m, leading to decreased proliferation and increased apoptosis in vitro. In vivo, cyclosporine decreased established rat monocrotaline-PAH. NFAT2 levels were increased in circulating leukocytes in PAH versus healthy volunteers. CD3-positive lymphocytes with activated NFAT2 were seen in the arterial wall in PAH but not normal lungs. The generalized activation of NFAT in human and experimental PAH might regulate the ionic, mitochondrial, and inflammatory remodeling and be a therapeutic target and biomarker.

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Dichloroacetate improves posts ischemic function of hypertrophied rat hearts.


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Comment in:


OBJECTIVES: We sought to determine whether improving coupling between glucose oxidation and glycolysis by stimulating glucose oxidation during reperfusion enhances posts ischemic recovery of hypertrophied hearts. BACKGROUND: Low rates of glucose oxidation and high glycolytic rates are associated with greater postischemic dysfunction of hypertrophied compared with nonhypertrophied hearts. METHODS: Heart function, glycolysis and glucose oxidation were measured in isolated working control and hypertrophied rat hearts for 30 min before 20 min of global, no-flow ischemia and during 60 min of reperfusion. Selected control and hypertrophied hearts received 1.0 mmol/liter dichloroacetate (DCA), an activator of pyruvate dehydrogenase, at the time of reperfusion to stimulate glucose oxidation. RESULTS: In the absence of DCA, glycolysis was higher and glucose oxidation and recovery of function were lower in hypertrophied than in control hearts during reperfusion. Dichloroacetate stimulated glucose oxidation during reperfusion approximately twofold in both groups, while significantly reducing glycolysis in hypertrophied hearts. It also improved function of both hypertrophied and control hearts. In the presence of DCA, recovery of function of hypertrophied hearts was comparable to or better than that of untreated control hearts. CONCLUSIONS: Dichloroacetate, given at the time of reperfusion, normalizes postischemic function of hypertrophied rat hearts and improves coupling between glucose oxidation and glycolysis by increasing glucose oxidation and decreasing glycolysis. These findings support the hypothesis that low glucose oxidation rates and high glycolytic rates contribute to the exaggerated posts ischemic dysfunction of hypertrophied hearts.

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