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Acute Hyperglycaemia Induces Alterations To Contractile Responses Of The Murine Pulmonary Artery And Aorta

Pulmonary arterial hypertension (PAH) is a progressive disorder characterised by pulmonary vascular constriction and remodelling which ultimately leads to right heart failure. Recent evidence suggests an association between type 2diabetes (T2D) and PAH. Epidemiological data show that patients with T2D are at increased risk of developing PAH(1). Clinically, PAH patients have increased insulin resistance(2), while experimentally, rodent models of insulin resistance develop PAH(3, 4). The aim of this study was to investigate the effects of acute hyperglycaemia on the contractile responses of isolated mouse intra-lobar pulmonary arteries (IPAs). In order to compare the pulmonary and systemic circulations we also investigated the effects of acute hyperglycaemia on contractile responses in isolated thoracic aorta.

Male mice (C57/BL6, 10 to 17 weeks old) were euthanased with a single intra-peritoneal injection of pentobarbitone (5mg/100g) and thoracicaorta (~600µm internal diameter)and IPAs (~250µminternal diameter) dissected free. Vessels were then incubated overnight in Krebs solution either at physiological glucose levels (5.6mM) or hyperglycaemic glucose levels (27.8mM). Tissue was mounted on a wire myograph and concentration response curve (CRCs) to endothelin-1 (ET-1, 0.1nM-10µM) produced. The hyperglycaemic contractile response to ET-1 was assessed in the presence of inhibitorsof protein kinase C (PKC;Go 6983, 10µM, 1 hour pre-incubation), reactive oxygen species (ROS; ascorbic acid, 100µM, 2 hour pre-incubation) and Rho Kinase (ROCK; fasudil hydrochloride, 10µM, 1 hour pre-incubation). E_{max} results are shown as a percentage of the maximal contraction to 60mM potassium chloride. Results are expressed as mean±S.E.M. Statistical analysis was carried out using a Students t-testor one way ANOVA followed by Dunnett's multiple comparison test, as appropriate.

Hyperglycaemia increased the efficacy of ET-1 in IPAs (E_{max}values: 127.2±12.1% to 292.7±7.9%, $P<0.001$, n=5) and aorta (184.2±24.6% to 486.6±19.5%, $P<0.001$, n=5), however, there was no effect on potency. The increased efficacy of ET-1 under hyperglycaemic conditions was attenuated by the ROCK inhibitor fasudilin both IPAs (217.6±3.2% to 160.8±4.3%, $P<0.001$, n=6) and aorta (210.4±4.3 to 153.0 ± 6.5%, $P<0.001$, n=6). Inhibition of PKC had no effect on the hyperglycaemicresponse within IPAs (178.1 ± 2.7% to 172.5 ± 5.2%,n=6), however, a significant reduction did occur in the aorta (248.3 ± 7.7% to 212.4 ± 2.1%, $P<0.01$, n=6). Inhibition of ROS did not have any effect on the hyperglycaemic response in either the IPAs (226.4 ± 32.5% to 214.6 ± 45%,n=6) or aorta (216.6 ± 22% to 204.1 ± 13.1%, n=6).

These results show that acute hyperglycaemia acts to increase the efficacy of the mouse IPA and thoracic aorta to ET-1. This increased contractile response is at least partially mediated through ROCK in IPAs and through ROCK and PKC in thoracic aorta.

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