

2-Aminoethyldiphenylborinate modifies the pulmonary circulation in pulmonary hypertensive newborn lambs partially gestated at high altitude

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Abstract

Calcium signaling through store-operated channels (SOC) is involved in hypoxic pulmonary hypertension. We determined whether a treatment with 2-aminoethyldiphenylborinate (2-APB), a compound with SOC blocker activity, reduces pulmonary hypertension and vascular remodeling. Twelve newborn lambs exposed to perinatal chronic hypoxia were studied, six of them received a 2-APB treatment and the other six received vehicle treatment for 10 days in both cases. Throughout this period, we recorded cardiopulmonary variables and on day 11 we evaluated the response to an acute hypoxic challenge. Additionally, we assessed the vasoconstrictor and vasodilator function in isolated pulmonary arteries as well as their remodeling in lung slices. 2-APB reduced pulmonary arterial pressure between the 3rd and 10th days, cardiac output between the 4th and 8th days, and pulmonary vascular resistance at the 10th day of treatment. The pulmonary vasoconstrictor response to acute hypoxia was reduced by the end of treatment. 2-APB also decreased maximal vasoconstrictor response to the thromboxane mimetic U46619 and endothelin-1 and increased maximal relaxation to 8-bromoguanosine 3',5'-cyclic monophosphate (8-Br cGMP). The maximal relaxation and potency to phosphodiesterase-5 and Rho-kinase inhibition with sildenafil and fasudil, respectively, were also increased. Finally, 2-APB reduced the medial and adventitial layers' thickness, the expression of α -actin, and the percentage of Ki67-positive nuclei of small pulmonary arteries. Taken together, our results indicate that 2-APB reduces pulmonary hypertension, vasoconstrictor responses, and pathological remodeling in pulmonary hypertensive lambs. We conclude that SOC targeting may be a useful strategy for the treatment of neonatal pulmonary hypertension; however, further testing of specific blockers is needed..