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Title: Dexamethasone induces anti-remodelling effects in rat pulmonary arterial smooth muscle cells

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Body: Inflammation is increasingly recognised in pulmonary arterial hypertension (PAH). Given that dexamethasone (dex) reverses PAH and pulmonary vascular remodelling in established rat monocrotaline (MCT)-induced PAH, we tested contributing mechanisms in pulmonary arterial smooth muscle cells (PASMC). Nuclear localisation of the p65 subunit of NF-κB was used as a marker of inflammation in MCT-exposed rats. Methods: PASMC from control and MCT 6-week old male Wistar rats were treated with increasing dex concentrations. Proliferation (3H-thymidine) and apoptosis (Hoechst nuclear staining; DNA fragmentation ELISA) assays were performed (n=5 per group). Immunohistochemistry for caspase 3 and p65 was performed on paraffin-embedded lungs from day 28 MCT-alone, MCT+dex-treated and control rats. Results: Dex reduced proliferation of PASMC at all concentrations with a maximal effect seen at 10-7M (3H-thymidine counts/minute 84997±6802 to 1993±3135, $p<0.0001$). Dex increased serum starvation-induced PASMC apoptosis as determined by Hoechst staining and DNA fragmentation in a time- and concentration-dependent manner, reaching a plateau after 72hrs with 10-7M dex (0.40±0.17 to 1.29±0.54, $p<0.001$). In rat lung, caspase immunostaining was increased in the PASMC layer in dex-treated MCT rats vs. MCT-alone controls (0 (0-40)% vs. 58.3 (1-100)%, $p<0.0001$). Finally, nuclear p65 was reduced in PASMC and endothelial cells in MCT-treated rats at all dex doses studied. Conclusion: Dexamethasone reduces proliferation and augments apoptosis in rat PASMC in vitro, and reduces activation of NF-κB within vascular cells. These actions, at least in part, may explain the reversal of PAH by dex seen in the rat MCT-PAH model.