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L-citrulline is protective in hyperoxic lung damage and improves matrix remodelling and alveolarization

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Moderate hyperoxia alters alveolar and vascular lung morphogenesis. Nitric oxide (NO) and matrix metalloproteinases (MMP) have a crucial role in the homeostasis of the matrix and bronchoalveolar structure and may be regulated abnormally by exposure to hyperoxia. Disruption of vascular endothelial growth factor (VEGF)-NO signaling impairs vascular growth and contributes to hyperoxia-induced vascular disease in bronchopulmonary dysplasia (BPD). We hypothesize that L-citrulline, by raising the serum levels of L-arginine and enhancing endogenous NO synthesis, might attenuate hyperoxia-induced lung injury in an experimental model of BPD. Neonatal rats (1 day old) were exposed to 60% oxygen or room air for 14 days and administered L-citrulline or a vehicle (sham). Lung morphometry were performed; Serum was tested for arginine level; Matrix metalloproteinases2 (MMP2) gene expression, VEGF gene and protein expression and endothelial NO synthase (eNOS) protein expression were compared.

Mean linear intercept was higher in the hyperoxia and sham groups when compared with the room air (RA) and L-citr+hyperoxia treated group (p<0.02). Secondary crests number was higher in L-citrulline treated and RA when compared to hyperoxia and sham group (p<0.02). L-Arginine level rose in the L-citrulline-treated group (p<0.05). L-citrulline did not affect MMP2 gene expression, but it regulated the MMP2 active protein, which rose in bronchoalveolar lavage fluid (p<0.05), presumably due to a post-transductional effect.

Compared with RA controls, hyperoxia significantly decreased VEGF and eNOS protein expression. At the same time, an increased lung VEGF gene and protein expression (p<0.05) were also seen in the rats treated with L-citrulline. We conclude that: (i) hyperoxia decreases growth and disrupts VEGF-NO signaling of lung; (ii) the main effects of L-citrulline are an increased serum level of arginine, as a promoter and a substrate of the nitric oxide synthase; and (ii) a better alveolar growth and matrix control than in hyperoxia-induced lung damage seems promising.

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