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Modulation of α_4 integrin mRNA levels is coupled to deficits in vasomotor function in rat arterioles by allylamine

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Abstract

Allylamine, a selective cardiovascular toxin that induces oxidative stress, is known to alter expression of extracellular matrix and cell adhesion proteins that are central to arterial remodeling. Our goals were to determine whether AAM treatment in rats modulates integrin/matrix-dependent arteriolar function, and to what extent integrin expression correlated to these alterations. Integrins are transmembrane proteins that facilitate mechanical and molecular signaling between the extracellular matrix and cytoskeleton, and so are suitable candidates for involvement in phenotypic and functional alterations of smooth muscle in response to oxidative stress. Arg-Gly-Asp (RGD) and Leu-Asp-Val (LDV), two integrin-binding motifs found in ECM proteins such as collagens and fibronectin, are known to interact with integrins $\alpha_v\beta_3$ and $\alpha_4\beta_1$, respectively. Previously, we found that RGD containing peptides induce vasodilation through $\alpha_v\beta_3$, while LDV containing peptides induce vasoconstriction through $\alpha_4\beta_1$ of normal rat cremasteric arterioles. In allylamine-treated rats (AAM), the vasomotor response to LDV, but not RGD, was attenuated in a dose-dependent manner. To determine whether changes in integrin subunit mRNA levels correlated with these functional changes, we performed reverse transcription and Real-time PCR for α_4 and β_3 integrin subunits on RNA isolated from single, first-order cremasteric arterioles. AAM treatment caused a dose-dependent decrease in α_4 mRNA expression, but not β_3 mRNA expression, suggesting that the changes in vasomotor activity to LDV peptides may be attributable in part to reduced α_4 expression upon exposure to AAM.