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**INTERMEDIN VIA AM1-RECEPTOR SIGNALLING
PROTECTS HUMAN VASCULAR AND CARDIAC
NON-VASCULAR CELLS FROM
ISCHAEMIA-REPERFUSION INJURY**

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Introduction Intermedin (IMD) protects the rodent cardiovascular system from ischaemia. Reperfusion after acute coronary syndrome augments cellular damage. It is not known if IMD benefits human cardiovascular cells during reperfusion injury.

Aims To examine (i) expression of IMD relative to the related peptide, adrenomedullin (AM), and their receptor components in adult human cardiovascular cells; (ii) cardioprotective effects of IMD in response to simulated ischaemia-reperfusion injury—effects of IMD given throughout the insult period were compared with administration of IMD during reperfusion alone; (iii) involvement of Calcitonin Receptor-Like Receptor (CRLR)/Receptor Activity-Modifying Proteins (RAMPs) in protective actions of IMD.

Methods IMD and receptor component expression were studied in human aortic endothelium (HAEC), smooth muscle (HASMC), cardiac microvascular endothelium (HMVEC), adult human ventricular cardiomyocytes (v-HCM) and fibroblasts (v-HCF); receptor subtype-involvement in protection by IMD (1 nmol l⁻¹) against injury by simulated ischaemia (100% N₂, pH 5.8, 20 mmol l⁻¹ 2-deoxyglucose and 4 mmol l⁻¹ KCl) and reperfusion were investigated using receptor component-specific siRNAs.

Results IMD, CRLR and RAMP1-3 were expressed in all cell types. IMD present throughout ischaemia (3 h) and reperfusion (1 h) attenuated injury ($p < 0.05$) versus those in the absence of IMD. When IMD was present during reperfusion only, protection was still evident ($p < 0.05$). Cytoskeletal disruption and protein carbonyl formation followed similar patterns. Pre-treatment (4 days) of HAEC and HCM with CRLR or RAMP2 but not RAMP1 or RAMP3 siRNAs, abolished IMD protection against ischaemia-reperfusion injury.

Conclusions IMD protects human vascular and cardiac cells from ischaemia-reperfusion, predominantly via AM1 receptors.