253 **REMOTE ISCHAEMIC PRECONDITIONING IS MEDIATED VIA THE SDF 1A/CXCR4 SIGNALLING AXIS**

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Background Ischaemic preconditioning is one of the most potent experimental modalities known to decrease infarct size following ischaemia-reperfusion (IR) injury. Much interest has been stimulated by the phenomenon of Remote Ischaemic Preconditioning (RIPC) which occurs when a preconditioning stimulus is applied to a limb remote from the heart to stimulate cardioprotection. The protection is believed to be mediated by an unidentified humoral factor between 3.5 and 30 kDa. Stromal cell-derived factor-1α (SDF-1α or CXCL12) is a chemokine of 10 kDa that is induced by hypoxia and recruits stem cells. However it also exerts a direct and acute cardioprotection via its receptor, CXCR4.

Aims We hypothesized that SDF-1α is a potential mediator of RIPC-induced protection.

Methods and Results Rats were anaesthetized and subjected to RIPC, consisting of 3 cycles of 5 minutes ischaemia by application of a tourniquet around the hind limb followed by 5 minutes of reperfusion. SDF-1α levels in rat plasma were measured using an ELISA kit. There was a 50% increase ($p<0.01$) in SDF-1α levels in plasma obtained from rats subjected to RIPC (890±70 pg/ml, n=8) compared to the control group (590±50 pg/ml, n=8). Pharmacological inhibition using AMD3100, a highly specific antagonist of CXCR4 signalling, was used to investigate the involvement of SDF-1α in RIPC. Rats were treated intraperitoneally with AMD3100 (10 μg/kg), prior to the RIPC protocol. The hearts were then excised and subjected to IR injury using the in vitro isolated Langendorff perfusion model. RIPC decreased the infarct size from 53±3% to 27±3% (n=6, $p<0.05$). Cardioprotection was abolished by AMD3100 (40±4% vs 53±3%, n=6, $p<0.05$). In separate experiments using myocytes isolated from rat hearts, SDF-1α was shown to reduce cell death, as measured by propidium iodide, following 3 h hypoxia and 1 h re-oxygenation (20±5 % vs. 34±5%). RIPC also improved functional recovery of cardiac papillary muscle from 53 ±13% (n=4) to 84±5% (n=6, $p<0.05$) and was similarly blocked by AMD3100 (46±7%, n=6). Further, the direct application of SDF-1α was shown to be protective in this model (89±9% vs. 55 ±9% control, n=4, $p<0.05$) and was blocked by AMD3100 (60 ±11%). We also measured the serum levels of dipeptidase (DPPIV) which is known to cleave and inactivate SDF-1α. We observed no change in DPPIV activity after RIPC. This suggests that increased synthesis and release of SDF-1α caused the increase in plasma levels.

Conclusion RIPC increases circulating levels of SDF-1α, which acts via the CXCR4 receptors in the heart to attenuate IR injury. These results suggest that this chemokine might be an essential mediator of RIPC.