Intrathecal morphine (ITM) can protect the heart against ischaemia reperfusion injury (IRI) by activating spinal but not peripheral opioid receptors. This study examined the mechanisms through which this protection may be signalled. An open chest rat model of IRI was used with an indwelling polyethylene catheter placed into the subarachnoid space 3 days before experimentation. Fifteen minutes prior to the ITM preconditioning, antagonists were given intravenously to evaluate the role of adenosine, bradykinin, calcitonin gene related peptide (CGRP) receptors as well as the autonomic pathway. Groups of animals (n=6/group) were, respectively, given the polar adenosine receptor antagonist 8-(p-sulfophenyl)theophylline (8-SPT), the bradykinin B2 antagonist HOE-140, CGRP fragment 8-37, and the nicotinic receptor blocker hexamethonium bromide (HEX) in a randomised order. Intrathecal saline infusion was used as control. The adenosine blocker 8-SPT was also given intrathecally as spinal opioids are known to induce local adenosine release. ITM preconditioning was induced with 3μg/kg morphine immediately before 30 minutes of ischaemia in the territory supplied by the left coronary artery and 120 minutes reperfusion. The hearts were then excised and the infarct size as a percentage of the area at risk (IS/AAR) was determined by triphenyltetrazolium and Evan Blue staining. The groups were comparable in terms of haemodynamics at baseline and the area at risk. The IS/AAR in the control group was 57±3% compared with 25±5% in the ITM group (P<0.01). The addition of 8-SPT, HOE-140, CGRP fragment 8-37, and HEX intravenously abolished the anti-infarct effect of ITM (41±8%, 52±10%, 56±9%, 51±6%, p<0.01 respectively compared with ITM). Interestingly, the intrathecal administration of 8-SPT, which does not cross the blood brain barrier, also blocked the effects of ITM (45±7%). The sole administration of any one of the antagonists did not alter infarct size compared with control. These results indicate that ITM can remotely protect the myocardium through a neural pathway and may involve multiple types of non opioid receptor activation. Spinal adenosine may be involved in the signalling process within the intrathecal space. However, these results do not preclude other mechanisms contributing to the preconditioning effect.

1. Wong GTC et al Anesthesia & Analgesia 2009 (Epub)