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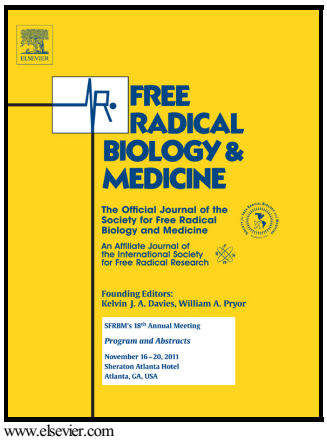

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Melatonin prevents secondary intra-abdominal hypertension in rats possibly through inhibition of the p38 MAPK pathway

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Running title: secondary intra-abdominal hypertension

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Abstract: Exogenous administration of melatonin has been demonstrated to down-regulate inflammatory responses and attenuate organ damage in various models. However, the salutary effect of melatonin against secondary intra-abdominal hypertension (IAH) remains unclear. This study sought to test the influence of melatonin on secondary IAH in a pathophysiological rat model and the underlying mechanisms involved. Before resuscitation, male rats underwent a combination of induced portal hypertension, applying an abdominal restraint device, and hemorrhaging to mean arterial pressure (MAP) of 40 mmHg for 2 h. After blood reinfusion, the rats were treated with lactated Ringer solution (LR) (30 mL/h), melatonin (50 mg/kg) +LR, and SB-203580 (10 μmol/kg)+LR. LR was continuously infused for 6 h. MAP, the inferior vena cava pressure and urine output were monitored. Histopathological examination, immunofluorescence of tight junction proteins, and transmission electron microscopy were administered. Intestinal permeability, myeloperoxidase activity, malondialdehyde, glutathione peroxidase, and levels of TNF-a, IL-2, and IL-6, were assessed. The expression of extracellular signal-regulated kinase, p38, c-Jun NH2-terminal kinase, translocation of nuclear factor kappa B subunit, signal transducers and activators of transcription and tight junction proteins were detected by Western blot. We found that melatonin inhibited the inflammatory responses, decreased expression of p38 MAPK, attenuated intestinal injury, and prevented secondary IAH. Moreover, administration of SB203580 abolished the increase in p38 MAPK and also attenuated intestinal injury. These data indicate that melatonin exerts a protective effect in intestine in secondary IAH primarily by attenuating the inflammatory responses which are in part attributable to p38 MAPK inhibition.