Leumedin (NPC-15669) Ameliorates Ischemia-Reperfusion Injury in Rat Lung Transplantation

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Abstract: Background: Neutrophil-mediated reperfusion injury has been demonstrated to contribute to early graft dysfunction after lung transplantation. NPC-15669, a member of a new class of anti-inflammatory compounds termed "leumedins", is known to block inflammation in several animal models. This agent specifically prevents the recruitment of neutrophils to inflammatory sites and inhibits subsequent tissue damage by inhibiting the cellular response to cytokine activation. As a result, the upregulation of CD11b/CD18 (Mac-1) on the neutrophils is inhibited. In the present experiment, we studied the effect of NPC-15669 on reperfusion injury in an orthotopic left lung transplant model in syngeneic Fischer rats.

Methods: Fifteen rats were divided into three groups. Group Ⅰ (n=5) rats underwent immediate graft implantation. Donor lungs for group Ⅱ (n=5) and group Ⅲ (n=5) underwent 18 hours of hypothermic ischemia (1℃) before implantation. All donor lungs were flushed with 20 ml of low-potassium dextran-1% glucose (LPDG) solution and stored at 1℃ until implantation. In group Ⅲ, 1 mg NPC-15669 was added to the last 1 ml of flush. In addition, the rats in group Ⅲ received NPC-15669 (10 mg/kg) intravenously (i.v.) prior to reperfusion. Groups Ⅰ and Ⅱ received an equivalent volume of normal saline i.v. Immediately prior to sacrifice at 24 hours after reperfusion, the function of the isolated graft was determined by an arterial blood gas (ABG) analysis. The neutrophil CD11b expression was determined by flow cytometry while isograft neutrophil sequestration was measured by a myeloperoxidase (MPO) assay.

Results: NPC-15669 significantly improved the PaO_2 levels compared with group Ⅱ (339.9±60.1 versus 52.5±3.0 mmHg, $p<0.001$). The CD11b expression in all groups increased in comparison to normal rats. The up-regulation of the CD11b expression in the NPC-15669 treated recipients decreased in comparison to the 18-hour storage control group (39.1±1.9 versus 53.0±4.5 mean fluorescence intensity, $p<0.01$). The graft myeloperoxidase activity significantly decreased in group Ⅲ (group Ⅱ versus group Ⅲ, 0.291±0.033 versus 0.172 ± 0.041 ΔOD/mg/min, $p<0.05$).

Conclusion: These results suggest that NPC-15669 reduced the degree of neutrophil mediated reperfusion injury and improved the post-transplant lung graft function.

Key words: Ischemic reperfusion injury, NPC-15669, Rat lung transplantation, Mac-1