原 著

Protective Effect of N-methyl-1-deoxynojirimycin on Lung Ischemia Reperfusion Injury: An in vivo Study

— MdNM Reduces Lung Ischemia Reperfusion Injury —

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Abstract

Purpose: The warm ischemic period following cardiac arrest damages the lungs. N-Methyl-1-deoxynojirimycin (MdNM) can preserve glycogen and reduce myocardial infarct size in rabbit heart. We tested the hypothesis that MdNM may reduce ischemia reperfusion injury of the lung using an in vivo rat model.

Methods: We administered MdNM (30mg/kg) or saline intravenously. We clamped the left lung hilus for 60 minutes and then reperfused it for 60 minutes. We measured baseline arterial oxygen tension and calculated the percent recovery of the oxygen tension every 10 minutes during reperfusion.

Results: The percent recovery of oxygen tension was significantly higher ($p < 0.05$) in the MdNM group ($n = 6$) than in the control group ($n = 6$) at the end of the 60 minutes of ischemia and during the initial 30 minutes of reperfusion. The oxygen tension was still higher in the MdNM group at the end of the 60-minute reperfusion, but the difference was not significant.

Conclusion: Preischemic treatment with MdNM had a partial but significant protective effect against ischemia reperfusion injury of the lung.

Key words : Lung ischemia reperfusion injury, Lung transplantation, Preconditioning, N-methyl-1-deoxynojirimycin

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Introduction

Shortage of donor organs is a major problem concerning lung transplantation. One way to increase the potential supply is to consider transplantation of lungs from cadaver donors. To do so, however, we have to overcome the challenges of prolonged warm ischemic time following cardiac arrest. Preischemic treatment with N-methyl-1-deoxynojirimycin (MdNM), an α-glucosidase inhibitor, preserves glycogen, decreases the accumulation of lactate, and reduces myocardial infarct size in rabbit heart.[1,2] MdNM works in rat liver, stomach, kidney and small intestine,[3,4] but its effect in the lung has not been studied. We hypothesized that pretreatment with MdNM would protect the lung against ischemia or reperfusion injury. We studied our hypothesis in an in-vivo rat model.

Materials and Methods

Twelve male Wistar rats weighing 270-330 g were housed in an air-conditioned room (25℃) with a 12-hr light-dark cycle and given food and water ad libitum. All experiments were conducted in accordance with Japanese Government Animal Protection and Management Law (No. 105). The rats were sacrificed while anesthetized.

The rats were randomly divided into two groups: a control group (n=6) and an MdNM group. They were

anesthetized by intraperitoneal administration of 50 mg/kg sodium pentobarbital and intramuscular injection of 0.01 mg atropine sulfate. Minimal supplementary doses of sodium pentobarbital were given when necessary. A 14-gauge cannula was inserted into the trachea for ventilation by a volume-controlled ventilator (model SN480-7; Shinano, Tokyo, Japan) with humidified room air at a tidal volume of 3.5 mℓ, a respiratory rate of 60 breaths/min, and a positive end-expiratory pressure of 3 cm H_2O. A 24-gauge cannula inserted into the femoral artery was used to monitor the arterial pressure, and a 22-gauge cannula inserted into the femoral vein was used to infuse agents. A left parasternal incision was performed. The inferior pulmonary ligament was divided, the left lung hilus was stripped, and an intravenous injection of 200 U heparin sodium was given. Saline (0.3 ml) or MdNM (30 mg in 0.3 ml saline) was intravenously injected, and 10 minutes later, left lung ischemia was established by clamping the left lung hilus. The tidal volume was reduced to 2.5 mℓ to prevent overexpansion injury of the right lung. After 60 minutes, the clamp was removed, and the left lung was reperfused and reventilated at a tidal volume of 3.5 mℓ. Mechanical ventilation was continued during the 60-minute reperfusion. Baseline arterial oxygen tension (Pa_{O_2}) was measured before the administration of saline or MdNM. Other arterial gas analyses were made at beginning of reperfusion and every 10 minutes during reperfusion. Each Pa_{O_2} measurement was expressed as a percentage of the baseline Pa_{O_2} as an index of function, and to determine the percent recovery of arterial oxygen tension ($\%Pa_{O_2}$). After 60 minutes of reperfusion, both the right and the left lungs were removed, weighed, dried at 84℃ for 72 h, and weighed again to calculate the wet to dry lung weight ratio.

The mean ± standard error of the mean was calculated, and an unpaired t-test was used to analyze differences between the 2 groups. A p value less than 0.05 was considered statistically significant.

RESULTS

Arterial pressure and heart rate did not change before or after the administration of saline or MdNM. Baseline arterial oxygen tension did not differ significantly between the control (118.8 ± 4.0 mmHg) and the MdNM groups (111.9 ± 4.4 mmHg). In both groups, $\%Pa_{O_2}$ decreased during clamping and recovered gradually during reperfusion. The $\%Pa_{O_2}$ in MdNM group was significantly higher than that in the control group during the initial 30 minutes of reperfusion (Figure). Forty minutes after the start of the reperfusion, the $\%Pa_{O_2}$ was still higher in the MdNM group but the difference was not significant. The wet to dry weight ratios of both the right and left lungs did not differ significantly between the control and the MdNM groups (data not shown).

Discussion

Despite in vivo experimental systems having the advantages of normal metabolism and less hemolysis, few in vivo studies on ischemia reperfusion injury in the lungs of rat have been reported.[5,6] To evaluate the lung function, we measured arterial oxygen tension, which is considered to be a good indicator of the function.[5] We strictly maintained constant body temperature, room temperature, and inspiratory air humidity, which resulted in a good stability of Pa_{O_2} value.

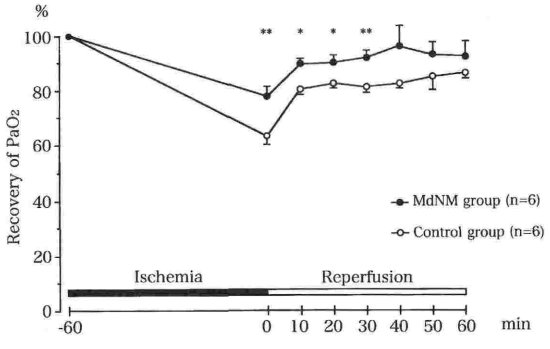

Figure. Recovery of arterial oxygen tension ($\%Pa_{O_2}$) as a percentage of baseline in the MdNM group (n = 6) and in the control group (n = 6) (mean± SEM). *p < 0.05. **p < 0.01.

MdNM had a partial but significant protective effect against ischemia reperfusion injury in the lung. The $\%Pa_{O_2}$ was higher in the MdNM group at the end of the 60 minutes of ischemia and during the initial 30 minutes of reperfusion. After 40 minutes of reperfusion, however, the $\%Pa_{O_2}$ was similar in both groups. We cannot deduce why MdNM only partially protected the lung. MdNM, an α-glucosidase inhibitor, preserves glycogen, decreases the accumulation of lactate, and reduces ischemia reperfusion injury in the heart[1,2]. We expected protective effect through the same mechanisms even in the lung. It is known that chemical preconditioning sometimes protects the heart, but not the lung[7]. It should be noted, however, that MdNM had a protective effect during the initial 30 minutes of reperfusion. This effect can probably be extended if the dose and time of MdNM administration are optimized. Actually, research is underway to achieve this by measuring the glycogen and lactate levels in both the right and left lung in the same animal model.

In conclusion, this preliminary study is the first to show that MdNM can partially protect the lung against ischemia reperfusion injury. Further studies are underway to optimize the effect of MdNM.

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