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Research Report

Neuroprotective effects of erythromycin on cerebral ischemia reperfusion-injury and cell viability after oxygen-glucose deprivation in cultured neuronal cells

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ABSTRACT

This study aims to determine if erythromycin has neuroprotective effects against transient ischemia and oxygen-glucose deprivation (OGD) in cultured neuronal cells. Sprague-Dawley rats were subjected to middle cerebral artery occlusion for 90 min, followed by reperfusion. The animals received a subcutaneous single injection of erythromycin lactobionate (EM, 50 mg/kg) or vehicle immediately after ischemia. Infarct volume, edema index, and neurological performance were evaluated at 24 and 72 h after reperfusion. Immunohistochemical analyses for oxidative stress (4-HNE, 8-OHdG) and inflammation (Iba-1, TNF-α) were conducted in the cortex at 24 h. Primary cortical neuronal cell cultures were prepared from the cerebral cortices of the animals and then subjected to OGD for 3 h. Ten or 100 μM EM was added before OGD to determine the effect of EM on cell viability after OGD. EM significantly reduced infarct volume ($p<0.01$) and edema volume ($p<0.05$) and improved neurological deficit scores ($p<0.05$) at 24 and 72 h. EM significantly suppressed the accumulation of 4-HNE ($p<0.01$) and 8-OHdG ($p<0.01$) and markedly reduced Iba-1 ($p<0.01$) and TNF-α expression ($p<0.01$). Treatment with 100 μM EM in vitro significantly reduced cell death after OGD. EM reduces neuronal damage following cerebral ischemia and OGD and may have antioxidant and anti-inflammatory effects.

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1. Introduction

Cerebral ischemia often kills or disables its victims. Neuroprotective therapy for acute cerebral ischemia is crucial for salvaging the ischemic penumbra and has become essential with the increasing use of thrombolysis (Pancioli *et al.*, 2008) and mechanical clot removal (Smith *et al.*, 2005). Most of the neuroprotective compounds so far developed for ischemic damage are clinically ineffective for acute stroke patients. The free radical scavenger NXY-059 was also ineffective for acute stroke patients in SAINT (Shuaib *et al.*, 2007). Only one free radical scavenger, edaravone, has been used clinically for neuroprotection in Japan (The Edaravone Acute Brain Infarction Study Group, 2003). The advent of new neuroprotective agents is urgently awaited.

Erythromycin (EM), meanwhile, has long been used as a macrolide antibiotic with few side effects. Pretreatment with clinical doses of erythromycin confers tolerance against hypoxia in vitro and cerebral ischemia in vivo (Huber *et al.*, 1999; Brambrink *et al.*, 2006; Koerner *et al.*, 2007).

This macrolide also influences inflammatory mechanisms in different organ systems (Labro and Abdelghaffar, 2001; Morikawa *et al.*, 2002).

We believe that EM holds great promise as a neuroprotective agent for acute ischemic damages.

To elucidate the neuroprotective effect of EM on neuronal damage, we administered the agent for transient focal ischemia using rats and cultured neuronal cells subjected to OGD.

2. Results

2.1. *Effect of EM in transient focal ischemia*

2.1.1. *Physiological variables*

There were no significant differences in pH, pCO_2, pO_2, rectal temperature (RT), mean arterial blood pressure (MABP), or blood glucose (BG) between the vehicle- and EM-treated groups after 24- or 72-h reperfusion, before or during MCAO (45 min after MCAO), or just before reperfusion (90 min after MCAO) (Table 1).

2.1.2. *MRI-CBF*

MCA occlusion reduced CBF in the territory supplied by the ipsilateral MCA at 90 min after MCA occlusion in both groups. The areas of decreased CBF were calculated based on the ipsilateral CBF, which was less than 60% of the mean value of the contralateral hemisphere. The mean area of the ipsilateral CBF reduction did not significantly differ between the vehicle and EM groups after 24 h ($56.1 \pm 9.0\ mm^2$ ($n=6$) vs $53.8 \pm 15.4\ mm^2$ ($n=6$)) (Fig. 1) or 72 h of reperfusion ($41.5 \pm 4.8\ mm^2$ ($n=5$) vs $45.4 \pm 12.5\ mm^2$ ($n=5$)). Hence, EM administration did not affect the CBF at 90 min.

2.1.3. *Infarct volume and edema index*

After 24 h of reperfusion, the infarct volume was significantly smaller in the EM-treated group ($n=6$) than in the vehicle-treated group ($n=6$) ($83 \pm 28.0\ mm^3$ vs $171.6 \pm 44.8\ mm^3$; 48.4% reduction vs vehicle mean; $p<0.01$) (Fig. 2A). After 72 h, the

Table 1 – Physiological parameters.

	24h					
	PH	pCO_2(mmHg)	pO_2(mmHg)	MABP(mmHg)	RT(°C)	BG(mg/dl)
before ischemia						
Vehicle	7.44±0.06	36.2±8.0	115.8±17.6	106±14	37.1±0.2	96±13
EM	7.43±0.03	29.6±7.7	122.9±13.6	135±14	37.2±0.2	107±13
45 min after ischemia						
Vehicle	7.40±0.07	32.6±5.7	114.8±19.7	111±28	37.2±0.1	98±8
EM	7.44±0.06	36.2±8.0	115.8±17.6	106±14	37.1±0.2	101±9
90 min after ischemia						
Vehicle	7.37±0.04	40.7±6.1	100.1±11.4	113±20	37.1±0.1	99±8
EM	7.40±0.05	37.5±5.5	105.8±8.4	97±21	37.2±0.1	94±7
	72h					
	PH	**pCO_2(mmHg)**	**pO_2(mmHg)**	**MABP(mmHg)**	**RT(°C)**	**BG(mg/dl)**
before ischemia						
Vehicle	7.37±0.07	37.9±7.5	108.2±9.1	118±22	37.1±0.1	96±13
EM	7.38±0.05	35.6±7.0	104.3±17.5	110±20	37.1±0.2	96±4
45 min after ischemia						
Vehicle	7.42±0.09	35.7±4.8	104.4±10.1	107±20	37.1±0.1	98±9
EM	7.39±0.05	32.1±7.7	109.7±20.0	118±19	37.1±0.2	92±5
90 min after ischemia						
Vehicle	7.45±0.08	36.3±5.3	112.3±19.6	103±21	37.1±0.1	100±5
EM	7.43±0.04	33.0±7.3	117.3±22.1	120±14	37.1±0.2	94±5

Values are the mean±S.D. There are no significant differences among the groups.
MABP, mean arterial blood pressure; RT, rectal temperature; BG, blood glucose

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