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BRAIN RESEARCH

Research Report

Post-ischemic treatment of pentoxifyline reduces cortical not striatal infarct volume in transient model of focal cerebral ischemia in rat

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ABSTRACT

Pervious studies reported that pentoxifylline (PTX) have a neuroprotective effect in the brain trauma and the global cerebral ischemia in the experimental models. However, the effect of PTX in transient model of focal cerebral ischemia has not been investigated yet. Therefore, this study was designed to investigate the effect of post-ischemic treatment of PTX on ischemic injuries in focal cerebral ischemic. Male Wistar rats ($n=32$) were assigned to control or PTX- (60 mg/kg i.p.) treated groups. PTX at dose 60 mg/kg i.p. administered at the beginning, or 1, or 3 h after ischemia. Focal cerebral ischemia was induced by middle cerebral artery occlusion, followed by 24-h reperfusion. At the end of 24 h ischemia, neurological dysfunction score was tested and infarct volumes were determined using triphenyltetrazolium chloride staining. Administration of PTX (60 mg/kg) at the beginning of ischemia, or 1, or 3 h after ischemia significantly reduces cortical infarct volumes by 43%, 40% and 41%, respectively. However, PTX did not significantly affect striatal infarct volumes and neurological dysfunction. The findings of the present study indicate that administration of PTX at least 3 h post-transient focal stroke reduces cortical brain ischemic damage in the rat model of transient focal cerebral ischemia.

1. Introduction

Pentoxifylline (PTX) is a drug that widely used for the treatment of intermittent claudicating, peripheral vascular and (Jacoby and Mohler, 2004) cerebrovascular disorders (Frampton and Brogden, 1995). Recent studies have reported that treatment with PTX reduces ischemic–reperfusion injuries in the lung (Thabut et al., 2001), intestine (Sener et al., 2001), liver (Iwamoto et al., 2002), kidney (Kim et al., 2001), and spinal cord (Savas et al., 2002). Moreover, PTX was shown to act as a neuroprotectant in brain trauma (Shohami et al., 1999), global ischemia (Sirin et al., 1998) and in hypoxic–ischemic brain injury in immature rats (Eun et al., 2000). In addition, our pervious studies have shown that PTX has a neuroprotective effect when administrated at 30 min before inducing focal cerebral ischemia (Nekoeian et al., 2005).

As far as the literature is concerned, almost no data about the effects of PTX on ischemic damage following transient focal cerebral ischemia are available. Therefore, the current study was conducted to investigate the effects of post-ischemic

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Table 1 – Physiological parameters including mean arterial pressure (MAP; mm Hg), pH, P_aCO_2 (mm Hg), P_aO_2 (mm Hg) in rats receiving 1 ml/kg normal saline (as control group) or pentoxifyline (PTX, 60 mg/kg i.p.) at 10 min before and 10 min after middle cerebral artery occlusion (MCAO)

Variables	10 min before MCAO		10 min after MCAO	
	Saline	PTX	Saline	PTX
pH	7.34±0.03	7.28±0.02	7.30±0.04	7.29±0.03
P_aCO_2	46±5	43±7	45±6	47±8
P_aO_2	92±8	88±9	84±10	89±14
MAP	91±7	85±4	90±9	87±4

Values are means±SEM.

treatment of PTX on cortex, striatum damage, and neurological deficit in rat model of transient focal cerebral ischemia.

2. Results

2.1. *Physiological parameters*

There were no significant differences in mean arterial pressure (MAP), P_aCO_2, P_aO_2, and blood pH between control (saline, 1 ml/kg) and PTX-treated groups (Table 1).

2.2. *Effect of PTX on post-ischemic injuries*

The total infarct volume in control group animals was 214±13 mm^3. Treatment with PTX (60 mg/kg i.p.) at the beginning, at 1 or 3 h after MCAO significantly reduces infarct volume by 39% (130±16 mm^3, $p<0.001$), 34% (140±7 mm^3, $p<0.001$) and 30% (149±10 mm^3, $p<0.001$), respectively (Figs. 1 and 2A).

The cortical and striatal infarct volumes in control group were 156±11 mm^3 and 58±4 mm^3. Administration PTX (60 mg/kg i.p.) at the beginning, or 1 h, or 3 h after MCAO significantly reduces cortical infarct volume by 43% (88±10 mm^3, $p<0.001$), 40% (93±8 mm^3, $p<0.001$) and 41% (91±5 mm^3, $p<0.001$), respectively (Fig. 2B). Moreover, PTX did not significantly affect the striatal infarct volume, regardless of when it was given (Fig. 2C and Fig. 1, $p>0.05$). Moreover, PTX significantly reduced infarct area in sections of 2–6 when administrated immediately after induction of cerebral ischemia (Fig. 3). PTX-mediated neuroprotection is mainly seen in the posterior part of the MCA territory where cortical, i.e., penumbral, tissue predominates (Fig. 3).

2.3. *Effect of PTX on neurological deficits score*

In the saline-treated control group, the neurological deficit score was 1.86±0.13 at 24 h after MCAO (Fig. 4). Administration of PTX (60 mg/kg) at the beginning (1.38±0.18), at 1 h (1.29±0.18), or 3 h (1.43±0.20) after MCAO, did not significantly change the neurological deficits score (Fig. 4, $p>0.05$).

3. Discussion

The aim of this study was to evaluate the effects of post-ischemic treatment of PTX on ischemic damage and neurological deficit in a rat model of transient focal cerebral ischemia.

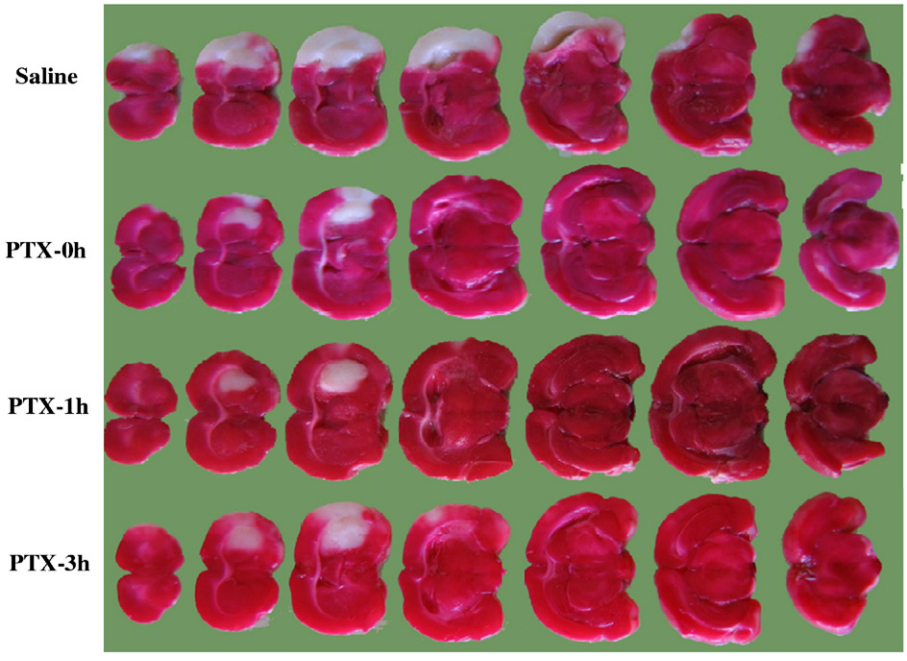

Fig. 1 – Photographs illustrating the in seven coronal sections of the rat brain with TTC staining, after 60-min MCAO and 23h reperfusion, in which red color is normal area and white color is infarct area. Colorless region corresponds to occluded MCA territory: (A) saline; (B, C, D) PTX (pentoxifyline) treated that were injected at the beginning (0 h), or at one (1 h) or three hours (3 h) after induction of ischemia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)