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BRAIN RESEARCH

Research Report

Post-treatment with selective beta1 adrenoceptor antagonists provides neuroprotection against transient focal ischemia in rats

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ABSTRACT

We have reported the neuroprotective effects of pre-treatment with β-adrenoceptor antagonists on the cerebral infarction at 1 and 7 days after focal ischemia in rats. However, the protective effect of post-treatment with β-adrenoceptor antagonists has not been investigated yet. This study was conducted to evaluate the post-treatment effects of selective β_1-adrenoceptor antagonists in the rat focal cerebral ischemia. Halothane anesthetized, normothermic adult male Sprague–Dawley rats were subjected to 2 h of middle cerebral artery occlusion (MCAO) using the intraluminal suture technique confirmed by laser Doppler flowmetry. Rats received intravenous infusion of saline 0.5 mL/h, esmolol 200 μg/kg/min, or landiolol 50 μg/kg/min (n=8 in each group). Infusion was initiated 30 min after MCAO and continued for 24 h. Rats were allowed to survive for 7 days, and the neurological deficit score was evaluated at 1, 4 and 7 days after reperfusion. The brains were removed and stained with triphenyltetrazolium chloride at 7 days after reperfusion. Neurological deficit scores were lower in the rats treated with esmolol or landiolol, compared with saline-treated rats at 1 day as well as 4 and 7 days. The infarct volumes of cortical and striatum were less in the rats receiving β-adrenoceptor antagonists than in saline-treated rats (P<0.05). The current study indicates that administration of selective β1-adrenoceptor antagonists after the onset of ischemia also improved neurological and histological outcomes following transient focal cerebral ischemia in rats.

1. Introduction

Treatment for acute stroke is usually provided after occurrence of ischemia. However, most of previous experimental studies have investigated the effect of only the pre-treatment for ischemia, although some studies reported the results of post-ischemic treatment (Furuichi et al., 2003; Vakil and Zahedi khorasania, 2007). Although many pharmacological agents are existed, it is an important thing that these agents could have neuroprotection even post-administration after stroke (Baron et al., 1995). Thus, therapeutic time window is important for the treatment of acute brain ischemia.

Recently, we have shown that selective β1 adrenoceptor antagonists, esmolol and landiolol, provided neuroprotection against transient focal cerebral ischemia and spinal ischemia in rats (Goyagi et al., 2006; Umehara et al., 2010). These protective effects were revealed as a result of the administration before ischemia (Goyagi et al., 2006; Umehara et al., 2010)

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because selective β1 adrenoceptor antagonists were started to be infused 30 min before ischemia, and was continued for 24 h in the study. Therefore, we conducted this study to examine whether post-administration of selective β1 adrenoceptor antagonist would provide neuroprotection against transient focal ischemia in rats.

2. Results

2.1. Physiological parameters

No significant differences among the experimental groups were detected in physiological data (arterial blood pressure, heart rate, $PaCO_2$, PaO_2, pH, temporalis muscle temperature, rectal temperature, blood glucose and hemoglobin concentrations) at baseline, during MCAO, and at reperfusion (Table 1). There were no significant differences among groups in weight change 1 and 7 days after ischemia. LDF signals showed similar changes in the treatment groups, as compared with saline-treated rats (Fig. 1).

2.2. Neurological deficit scores

Neurological deficit scores were significantly lower in esmolol- and landiolol-treated rats than in the saline-treated rats at 1, 4 and 7 days after ischemia, whereas there were no significant differences in neurological deficit scores between esmolol and landiolol groups (Table 2).

2.3. Infarct volume

TTC-determined infarct volumes in the cortex and striatum at 7 days after reperfusion were significantly less in rats treated with esmolol or landiolol, when compared with saline-treated rats ($P<0.05$, Fig. 2). However, there were no significant differences in the infarct volume between the esmolol- and landiolol-treated rats.

Table 1 – Neurological deficit score.

Assessment Item	Score
Level of consciousness	
Normal (alert)	0
Stuporous	5
Comatose	15
Sensorimotor function	
No withdrawal in response to pain	0
Front paw	2
Back paw	2
No righting reflex	10
Gait	
Normal	0
Moderate ataxia	5
Able to stand	10
Unable to stand	15
Behavior	
No grooming	6
No eating	10
No exploratory behavior	10

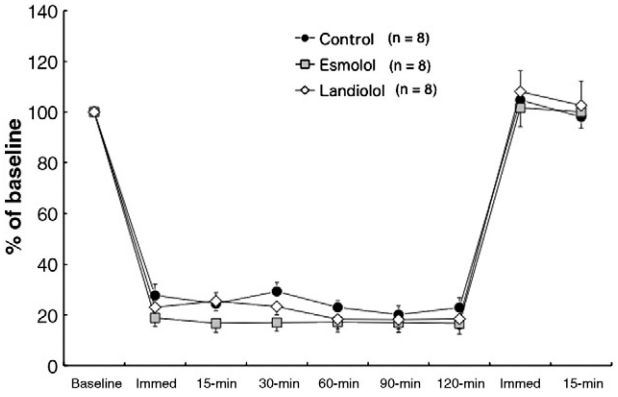

Fig. 1 – Residual LDF signals during 2 h of middle cerebral artery occlusion (MCAO) and 15 min of reperfusion, expressed as percentages of pre-ischemic baseline signal in rats treated with saline (control, *n*=8), esmolol (*n*=8), and landiolol (*n*=8) (mean±SEM). Treatment was started 30 min after the beginning of MCAO and was continued until 24 h of reperfusion. LDF signals decreased to the same extent during MCAO in all groups.

3. Discussion

In this study, we have demonstrated that post-treatment with selective β1 adrenoceptor antagonists for transient focal ischemia reduced the infarct volume and neurological deficit score 7 days after ischemia. This finding suggests that post-ischemic administration of selective β1 adrenoceptor antagonists provided the neuroprotective effects.

Several β adrenoceptor antagonists have been shown to provide brain protection in in vivo studies (Little et al., 1982; Capraro et al., 1984; Latchaw et al., 1985; Standefer and Little, 1986; Savitz et al., 2000). Propranolol, even D-propranolol, has been demonstrated to exert neuroprotection against focal ischemia in cats (Latchaw et al., 1985). Carvedilol, an α and β antagonist, also has been demonstrated to reduce the infarct volume and improve the neurological outcome by decreasing TNF-α and IL-1β levels after focal ischemia in rats (Savitz et al., 2000). We have reported that selective β1 adrenoceptor antagonists, esmolol and landiolol, had neuroprotection after transient focal cerebral ischemia (Goyagi et al., 2006) and spinal ischemia (Umehara et al., 2010) in rats. However, the protective drugs were administrated before ischemic insults in all studies (Savitz et al., 2000; Goyagi et al., 2006; Umehara et al., 2010). In clinical situations, no protective drugs can be given before acute stroke. The only thing that we can do in acute stroke is to give immediately any protective drugs or procedures to the patients who developed stroke. Therefore therapeutic time window is very important in acute stroke (Baron et al., 1995; Segura et al., 2008; Ginsberg, 2008). Endogenous catecholamine level increases after acute stroke (Cubeddu and Hoffman, 1987), while administration of β adrenoceptor antagonists decreases catecholamine level (Svendsen, 1983). Therefore, it is reasonable to administer β adrenoceptor antagonists to the patients who developed acute stroke, since administration of β adrenoceptor antagonists could improve outcome and mortality in serious head injury