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A Study on Cerebral Ischemia-Reperfusion Injury: Involvement of Platelet-Activating Factor

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ABSTRACT

To elucidate involvement of platelet-activating factor (PAF) in cerebral ischemia-reperfusion injury, male Sprague-Dawley rats and albino mice of either sex were subjected to a 10-min bilateral carotid artery occlusion and 6-hr recirculation. The McGraw stroke index in mice was markedly inhibited by PAF antagonists, BN 52021 and CV 6209 (1 mg/kg, i.p., each) When they were administered 10 min before bilateral carotid artery occlusion or 1 hr after reperfusion. The increases in brain water content were significantly attenuated by treatment with BN 52021 or CV 6209 in both animals. BN 52021 exhibited a significant improvement in the postischemic blood pressure change in association with a beneficial effect on the delayed dilatation of pial arterioles after 10 min of ischemia. Thus it is suggested that PAF plays an important role as an endogenous mediator in development of cerebral ischemia-reperfusion injury, and further, specific antagonists to PAF will be able to prevent or reverse the pathological sequelae of cerebral ischemia.

Key Words: Platelet-activating factor, Cerebral ischemia-reperfusion, Pial arteriole

INTRODUCTON

Cerebral ischemia is one of the most frequent and fatal disorders that affect on the central nervous system. A number of bioactive substances have been proposed to play a role in mediation of ischemic cerebral failure: catecholamines, serotonin, angiotensin, histamine, cytokines, thrombin and oxygen free radicals (Demopoulos *et al.*, 1984; Moskowitz *et al.*, 1975; Unterberg *et al.*, 1986).

Recently, a potential role for platelet-activating factor (PAF) in neuronal function was suggested by Kornecki *et al.* (1988). PAF is a phospholipid mediator of allergy and inflammation with numerous biological actions (Braquet *et al.*, 1987). Exogenous administration of PAF to laboratory animals can cause acute circulatory collapse, and death (Bessin *et al.*, 1983; Blank *et al.*, 1979). PAF was demonstrated to be one of the factors responsible for the irreversible neuronal degradation as associated with spinal cord injury, trauma, and stroke. Recent studies have demonstrated that PAF antagonists provide the enhancement of early neuronal recovery after brain ischemia (Kochanek *et al.*, 1987) and a protection against the damage induced by ischemiareperfusion in various organs (Braquet *et al.*, 1987; Spinnewyn *et al.*, 1988).

However, it is not well understood that PAF is involved in the pathogenesis of cerebral parenchymal damages and the alterations in cerebral vasomotion following cerebral ischemia-reperfusion. In the present study, it was aimed to elucidate involvement PAF in the brain injury.

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MATERIALS AND METHODS

Determination of stroke index

Albino mice (25~30 g) of either sex were anesthetized with ketamine (50 mg/kg, i.p.). A midline incision was made on the ventral surface of the neck and common carotid arteries were isolated for the later induction of ischemia by clamping. Animals were placed singly in their home cages after surgery and allowed to recover from anesthesia for 1 hr. After that time, the bilateral common carotid arteries were occluded with vascular clips to prevent blood flow for 10 min.

Morbidity and mortality were evaluated every hr until the sixth hr after declamping according to the stroke index chart defined by McGraw (1977): decrease in alertness and movement, weakness, ptosis, cocked head, circling behavior, hind limb splaying or rotation, seizures, and malaise as manifested by piloerection and tremor (Table 1). Each behavioral impairment was assigned a numerical weight used in calculating stroke index overall and at each evaluation. Drugs were administered intraperitoneally 10 min before or 1 hr after recirculation. In control group (sham-operated), all the surgical procedures were the same except for clamping.

Table 1. Numerical weight of behavioral impairments following cerebral ischemia

	Weight(S_i)
Hair roughed up or tremor	1
Obtunded	1
Paucity of movements	1
Head cocked	3
Eyes fixed open	3
Ptosis	2
Splayed out hind limb	3
Extreme rotation of hind limb	3
Circling behavior	3
Seizures	2
Rolling seizure	3
Extreme weakness (comatose)	6
Death	34
Stroke index score	(ΣS_i)

Determination of brain water content

Male Sprague-Dawley rats (220~280 g) and albino mice (25~30 g) of either sex were anesthetized with ketamine (50 mg/kg, i.p.). Operation was undertaken as described above. After a 10-min occlusion and 6 hr-reflow, animals were sacrificed by decapitation. The whole brain was removed from the skull, weighed, and then dried (48 hr at 70℃) for evaluation of water content. Percent water content was calculated as follows:

$$\text{Water}(\%)=\frac{\text{wet weight-dry weight}}{\text{wet weight}}\times 100$$

Intra-arterial blood pressure monitoring

Male rats were anesthetized with urethane (1 g/kg, i.p.) and placed on a heating pad to maintain body temperature at 37℃. After tracheostomy, rats were ventilated with a positive-pressure respirator (Narco Bio-systems, V5KG) and received gallamine triethiodide (5 mg/kg, i.v.) for skeletal muscle paralysis. Arterial blood pressure was monitored with a Statham pressure transducer (Gould, P23ID) connected to a canula introduced into the aorta via the left femoral artery. Blood pressure was recorded on the Biograph (Harvard) from 20 min before clamping to 6 hr after declamping. Arterial blood gas was determined at regular intervals and the respirator was adjusted to maintain PaO_2 at 35~45 mmHg.

Measurement of pial arteriolar diameter

The rat's head was fixed on a stereotaxic apparatus (Stoelting) and an open cranial window (4×4 mm) was made over the right parietal cortex using an air-cooled drill. The dura was left intact and the cranial window was filled with prewarmed artificial cerebrospinal fluid (37℃) with mineral oil overlying the dura. The cerebral microcirculation was visualized through a stereo microscope (Nikon, SMZ-2T) connected to a CCD video camera (Sanyo, VDC 3900) and a monitor. The diameter of pial arteriole was simultaneously measured by a video microscaler (FOR-A, IV-550) at a total magnification of 480x. The image was recorded to a video cassette recorder

(Hitachi, VT-S 730) for the storage and future replication. Drugs were administered intraperitoneally 10 min before bilateral carotid artery occlusion. The composition of artificial cerebrospinal fluid was as follows (in mM): NaCl, 125; KCl, 3.5; $CaCl_2$, 1.3; $MgCl_2$, 1.1; $NaHCO_3$, 25.

Drugs used

The drugs used in this study were BN 52021 (Institut Henri Beaufour, France) and CV-6209 (Takeda, Japan). All other chemicals were of the highest grade commercially available.

Statistical analysis

Data are expressed as means±SEM. Unpaired Student's t-test was used for statistical analysis except for the mean arterial blood pressure and pial arteriolar diameter, which were analysed by a repeated measures analysis of variance with post hoc analysis using Duncan's new multiple range test. Probability values (P) less than 0.05 were considered to be significant.

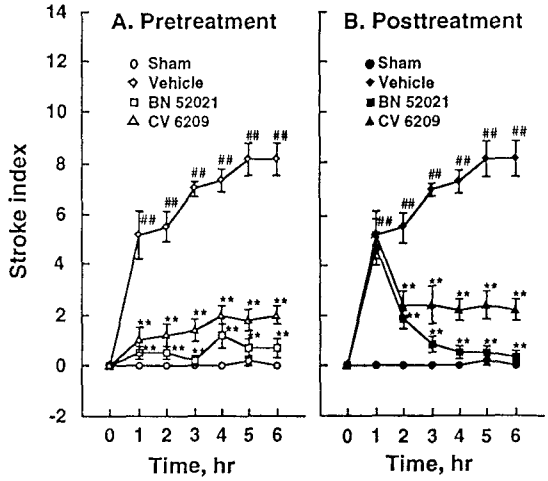

Fig. 1. Effect of PAF antagonists on stroke index. BN 52021 and CV 6209(1 mg/kg, each) were administered intraperitoneally 10 min before bilateral carotid artery occlusion (A, pretreatment) or 1 hr after recirculation (B, posttreatment). Clamp was released for reflow at 0 hr. ##, $p<0.01$ vs. sham group, **, $p<0.01$ vs. vehicle group.

RESULTS

Stroke index

The behavioral pattern of mice was highly impaired after bilateral carotid artery occlusion and reperfusion with a strong upward tendency in stroke index (Fig. 1). Almost all mice were dead within 3 hr of recirculation.

The stroke index was markedly inhibited by the intraperitoneal administration of BN 52021 (1 mg/kg) 10 min before bilateral carotid artery occlusion ($p<0.01$). This preventive effect was manifested from the first hr of reperfusion and led to a significant inhibition until the sixth hr onwards. Pretreatment with CV 6209 (1 mg/kg, i.p.) exhibited a significant inhibition of stroke index ($p<0.01$). When BN 52021 and CV 6209 were administered 1 hr after reperfusion, the stroke index was significantly decreased from the second hr of reperfusion ($p<0.01$) and sustained around the values of about 0.5 for BN 52021 and about 2.3 for CV 6209, respectively.

Brain edema

As shown in Table 2, brain water content of rats and mice were markedly increased by 10-min carotid occlusion and 6-hr recirculation ($p<0.01$ and $p<0.01$, respectively). Treatment with BN 52021 (1 mg/kg, i.p.) significantly decreased the brain water content to the corresponding levels of sham-operated groups ($p<0.01$ in rats; $p<0.01$ in mice). CV 6209 (1 mg/kg, i.p.) significantly attenuated the increase in brain water content ($p<0.01$ in rats; $p<0.05$ in mice).

Blood pressure

Bilateral carotid artery occlusion induced changes in mean arterial blood pressure: a transient increase followed by decrease in blood pressure (Fig. 2). Postischemic reperfusion also induced an initial transient increase in blood pressure followed by rapid decrease in blood pressure, resulting in death after 3 hr of recirculation.

Pretreatment with BN 52021 (1 mg/kg, i.p., 10 min before clamping of bilateral carotid arteries) significantly ameliorated the initial transient increase in blood pressure following postischemic

Table 2. Effect of pretreatment with PAF antagonists on brain water content (%) of animals subjected to cerebral ischemia-reperfusion injury

Animals	Sham	Pretreatments with		
		Vehicle	BN 52021	CV 6209
Rats	78.77±0.23	84.46±0.24††	79.38±0.21††	80.04±0.28**
Mice	72.72±0.23	77.09±0.23††	73.49±0.24**	74.12±0.28*

Mean±SEM (n=6). BN 52021 (1 mg/kg) and CV 6209 (1 mg/kg) were administered intraperitoneally 10 min before bilateral carotid artery occlusion. ††, $p<0.01$ vs. sham group. *, $p<0.05$; **, $p<0.01$ vs. vehicle group.

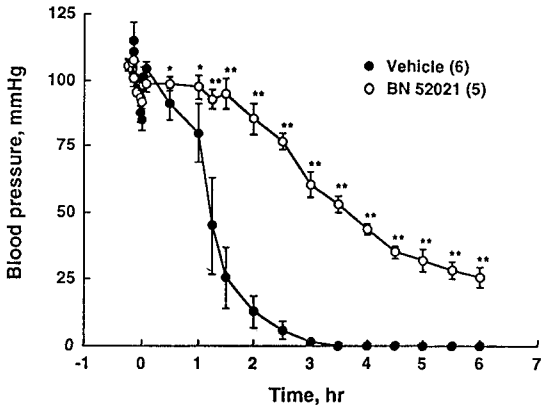

Fig. 2. Effect of pretreatment with BN 52021 on mean arterial blood pressure of rats that were subjected to cerebral ischemia-reperfusion. BN 52021 (1 mg/kg, i.p.) was administered 10 min before clamping of bilateral carotid arteries. Closed circles indicate the vehicle group, and open circles indicate the BN 52021-treated group. Numbers in parentheses represent the numbers of experiments. *, $p<0.05$; **, $p<0.01$, compared with the corresponding value of vehicle group.

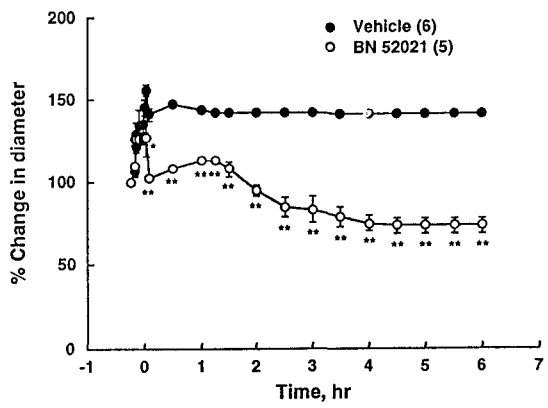

Fig. 3. Protective effect of BN 52021 on the changes in rat pial arteriolar diameter during cerebral ischemia-reperfusion. BN 52021 (1 mg/kg, i.p.) was administered 10 min before clamping of bilateral carotid arteries. Closed circles indicate the vehicle group, and open circles indicate the BN 52021-treated group. Numbers in parentheses represent the numbers of experiments. *, $p<0.05$; **, $p<0.01$, compared with the corresponding value of vehicle group.

reperfusion ($p<0.01$). Moreover, it maintained the mean arterial blood pressure around 100 mmHg during the period of 1.5 hr of recirculation, and thereafter, significantly inhibited the decline tendency in blood pressure ($p<0.01$), with prolonged survival time.

Pial arteriolar diameter

As shown in Fig. 3, bilateral common carotid artery occlusion caused a rapid increase in diameter of rat pial arterioles. Reperfusion by declamping caused a rapid and transient decrease in pial arteriolar diameter followed by a gradual and sustained increase. Pretreatment with 1 mg/kg of BN 52021 exhibited a marked protective effect against the delayed dilatation of pial arterioles during reperfusion after bilateral carotid artery occlusion ($p<0.01$).

DISCUSSION

In the present study, it was demonstrated that bilateral carotid artery occlusion and reperfusion caused severe impairment of behavioral function, brain edema, systemic hypotension, and alterations in cerebral vasomotion. These impairments were markedly improved by treatment with PAF antagonists.

PAF is an endogenous phospholipid of 1-o-alkyl-2-acetyl-sn-glycero-3-phosphocholine with diverse and potent biological activities including proinflammatory, hemostatic, and vasoactive effects in various tissues (Bourgain *et al.* 1985; Braquet *et al.*, 1987), and is known to be synthesized by neurons and in the injured brain (Braquet *et al.*, 1987, 1989; Yue *et al.*, 1990). Cerebral ischemia causes a breakdown of cellular lipids and an increase in the levels of free fatty acids in the brain (Bazan, 1970, 1991; Gaudet *et al.*, 1980; Yamamoto *et al.*, 1986). The cerebrovascular effects of exogenous PAF include disruption of the blood-brain barrier (Kumar *et al.*, 1988), edema formation (Humphrey *et al.*, 1982a), and vasospasm (Kochaneck *et al.*, 1988).

Clinical and experimental studies indicated that periods of hypoxia or disruption of blood flow result in impairments of neuronal function and behavioral disorders (Kochanek *et al.*, 1987). In this study, the stroke index of mouse indicated a severe behavioral disturbance after clamping of bilateral carotid arteries and recirculation. When BN 52021 (1 mg/kg, i.p.), the most active PAF antagonist of the ginkgolide series, was administered preventively, the mouse brain was protected from increase in stroke index. CV 6209 (1 mg/kg, i.p.), PAF antagonist, also significantly inhibited the stroke index with lesser ability of inhibition in comparison to BN 52021. This result was nearly identical to the report of Spinnewyn *et al.* (1988) in spite of some differences in the route of administration and dosage of BN 52021 and species of animal, suggesting that PAF plays an important role in development of cerebral ischemia-reperfusion injury.

It has been reported that PAF induces vascular hyperpermeability resulting in plasma extravasation (Braquet *et al.*, 1984; Humphrey *et al.*, 1982a, 1982b) and brain contains a considerable amount of phospholipids, such as alkylacylglycerol phosphocholine, the precursor of PAF, as well as relatively high levels of enzymes for synthesis and metabolism of PAF (Francescangeli and Goracci, 1989; Tokumura *et al.*, 1987). Inasmuch as brain edema is one of the most important clinical consequences of ischemic brain damage, we examined the influence of PAF antagonists on the brain edema following cerebral ischemia-reperfusion. In the present study, the increase in brain water content was significantly attenuated by BN 52021 and CV 6209 in rats and mice. Although the actual PAF concentration in edematous brain was not measured in this study, this result indicates that a large amount of PAF must have been produced in the brain tissue after cerebral ischemia-reperfusion, and that cerebral vascular permeability was increased by this PAF, resulting in brain edema. Therefore, our results support that PAF could be one of the most important factors involved in the pathogenesis of brain edema.

The hemodynamic effects of exogenous PAF are characterized by profound hypotension and perfusion changes that depend on the target organ. It was suggested that exogenous PAF acts directly both as a constrictor and dilator of cerebral vessels in vitro, depending on the vascular tone prior to PAF challenge (Uski and Reinstrup, 1990). Cerebral blood vessel has a segment-specificity or species-related differences in PAF sensitivity (Edwards *et al.*, 1991). Exogenous PAF has been demonstrated to reduce circulation and promote dysregulation of cerebral blood flow during systemic PAF challenge in newborn pigs, rats, and rabbits (Armsted *et al.*, 1988; Kochanek *et al.*, 1988; Lindsberg *et al.*, 1990). On the other hand, Kochanek *et al.* (1990) reported that two structurally unrelated PAF antagonists (BN 52021 and WEB 2086) had no influences on cerebral blood flow as well as on cerebral metabolic rate of oxygen in rats, and suggested that endogenous PAF does not modulate blood flow and metabolism in normal rat brain. However, Panetta *et al.* (1987) have reported that BN 52021 protected gerbil brain during postischemic reperfusion, in association with enhanced cerebral blood flow and reduced free fatty acid accumulation.

In the present study, we examined the effect of

BN 52021 on the changes in mean arterial blood pressure and pial arteriolar diameter of rats during cerebral ischemia-reperfusion. Interestingly, BN 52021 exhibited not only a significant improvement in the postischemic blood pressure change but also a beneficial effect on the delayed dilatation of pial arterioles after 10 min of ischemia. These findings strongly suggest that the cerebral circulatory deterioration associated with cerebral ischemia-reperfusion is ascribed to the potent cerebral vasodilatory and hypotensive actions of PAF produced during cerebral ischemia-reperfusion.

The action of PAF is known to be mediated through a specific receptor (Hwang *et al.*, 1983; Korth *et al.*, 1988; Lindsberg *et al.*, 1991), and the biochemical mechanism of action has been proposed to be relared to a rise in free intracellular Ca^{2+} (Kornecki and Ehrlich, 1988; Hirafuji *et al.*, 1988) and to the activation of phospholipase A_2 and phospholipase C (Aveldano and Bazan, 1975; Takayasu *et al.*, 1990). However, in the present study, it is hard to explain how PAF induced cerebral ischemia-reperfusion injury, and how the PAF antagonists (BN 52021 and CV 6209) exhibited the prophylactic and therapeutic effects on the deterioration of cerebral pial vessels and the impaired brain function and brain edema following cerebral ischemia-reperfusion. Additional studies remain to clarify the detailed pathophysiology of cerebral ischemia-reperfusion injury and the mechanism of beneficial actions of PAF antagonists. Taken together, these data support that PAF plays an important role as an endogenous mediator in pathological states such as stroke and brain injury, and specific PAF antagonists will be able to prevent or reverse the pathological sequelae of cerebral ischemia.

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= 국문초록 =

뇌의 허혈-재관류손상에 대한 연구: 혈소판활성인자의 관련

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이 원 석 · 임 병 용 · 홍 기 환

뇌의 허혈-재관류 손상에 있어서 혈소판 활성인자 (PAF, platelet activating factor)의 관련을 증명하기 위하여 흰쥐와 생쥐에서 양측 총경동맥을 10분간 결찰하고 그후 6시간동안 재관류시켜 허혈-재관류 손상을 야기시켰다. 생쥐에 PAF 길항제인 BN52021과 CV6209 (각각 1 mg/kg, i.p.)를 총경동맥결찰 10분전 또는 재관류 시작 1시간 후에 투여시 McGram stroke index는 심하게 억제되었다. 흰쥐와 생쥐에서 뇌허혈-재관류에 의한 뇌수분함량의 증가는 BN52021 또는 CV6209 전처치에 의하여 유의하게 억제되었다. BN52021 전처치는 허혈 후의 혈압변동을 개선시켰을 뿐만 아니라 뇌연막동맥의 확장지연에 대하여도 효과가 있었다. 이러한 실험결과로 보아 PAF가 뇌허혈-재관류 손상의 발생에 내인성 인자로서 중요한 역할을 하는 것으로 사료된다. 나아가 PAF 길항제가 뇌허혈후의 병리학적 후유증의 개선 내지는 예방에 사용될 수 있을 것으로 기대된다.