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Blood Flow Changes in the Optic Nerve Head of Albino Rabbits Following Intravenous Administration of Brovincamine Fumarate, an Improver of Cerebral Circulation and Metabolism

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Blood flow changes in the optic nerve head of normal, adult albino rabbits following intravenous administration of brovincamine fumarate (BV), an improver of cerebral circulation and metabolism, were investigated employing the hydrogen clearance method. In the BV (0.1 mg/kg)-administered group, the blood flow in the optic nerve head showed a gradual increase immediately after injection and reached a maximal value of $124.2 \pm 7.3\%$ against the value before injection at 20 min after injection, followed by a gradual decrease in blood flow. Statistical analysis showed a significant increase ($P < 0.05$) in blood flow at 10 to 40 min after injection, compared with the value before injection in the BV (0.1 mg/kg)-administered group, but no significant changes in blood flow were observed in either the BV (0.5 mg/kg)-administered group or the control group given no BV throughout the time course. No significant changes in the mean values of the mean blood pressure in the femoral artery, pulse rate, respiratory rate or rectal temperature were observed in any group throughout the experiment. These results indicate the different efficacy of the two doses to the relaxing action of the feeding vessels around the optic nerve head.

Key words: albino rabbits; brovincamine fumarate; cyclic AMP; hydrogen clearance method; optic nerve head blood flow

Brovincamine is a compound in which brovine is introduced at position 11 of vincamine, an alkaloid extracted from *vinca minor* L. Vincamine has been reported to reduce vascular resistance, leading to an increase in the cerebrovascular blood flow (Földi and Obál, 1965; Solti, 1965; Noguchi et al., 1992). Brovincamine is also expected to produce vasodilation through a blockade in the slow Ca^{2+} -channel (Katsuragi et al., 1984) and lead to an increase in the cerebrovascular blood flow (Kushiku et al., 1985). Brovincamine fumarate (BV, Sabromin, Sandoz/Sankyo Pharmaceutical Co., Tokyo, Japan) (Fig.1) is used in Japan mainly as an improver of cerebral circulation and metabolism, and also as an inhibitor of the aggregation of platelets through the cyclic AMP path-

way (Yasunaga, 1982). This agent dilates intracranial vessels more selectively than does nifedipine, another Ca^{2+} -channel blocker (Katsuragi et al., 1984; Kushiku et al., 1985) and seldom causes the adverse reactions induced by peripheral vasodilation, such as facial flushing and orthostatic hypotension (Sawada et al., 1996). Recently, oral BV therapy has been tried on patients with normal-tension glaucoma (NTG), with favorable results in the prevention of visual field defect progression (Koseki et al., 1994; Sawada et al., 1996) and the improvement of decreased retinal sensitivity (Hama et al., 1992). BV has shown little influence on the systemic blood pressure upon administration unlike the other Ca^{2+} -antagonists (Sugioka et al., 1982; Noguchi et al., 1992;

Abbreviations: BV, brovincamine fumarate; G, gauge; IOP, intraocular pressure; NTG, normal-tension glaucoma; PG I_2 , prostaglandin I_2

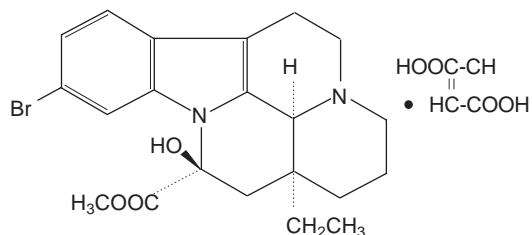


Fig. 1. Chemical structure of brovincamine fumarate.

Harino et al., 1992). This is considered useful for the treatment of patients with NTG, because systemic hypotension is one of the risk factors for glaucomatous damage to the optic nerve head (Kaiser and Flammer, 1991; Kaiser et al., 1993). However, little is known about the influence of BV on the optic nerve head circulation clinically or experimentally, although it is known that the selective relaxing action of this agent is most potent in isolated rabbit basilar arteries (Narita et al., 1986). In the present study, therefore, the blood flow changes in the optic nerve head of adult albino rabbits following intravenous administration of BV were investigated employing a hydrogen clearance method which allows subsequent and repeated measurements *in vivo* (Aukland et al., 1964).

Materials and Methods

Animals

The animal experiment reported here was done in accordance with the Guidelines for Animal Experiments at the Faculty of Medicine, Tottori University. We used 18 normal, adult albino rabbits (18 eyes) of both sexes, each weighing 2.9 to 4.2 kg, for measurements of the blood flow in the optic nerve head. Anesthesia was induced through an intramuscular injection of a mixture of ketamine hydrochloride (40 to 60 mg/kg) and xylazine hydrochloride (2 to 3 mg/kg). Further anesthesia was maintained with 2 or 3 supplemental injections of pentobarbital sodium (25 mg/kg; maximally 300 mg in total volume) into the auricular vein. Throughout the experiment, the femoral artery was cannulated with a catheter connected to a pressure

transducer to monitor the pulse rate and mean blood pressure. Further, the respiratory rate and rectal temperature were measured routinely.

Measurements of blood flow in the optic nerve head

Blood flow in the optic nerve head was measured according to the hydrogen clearance method first reported by Aukland and others (1964), as illustrated in Fig. 2. Each measurement was performed by initially forcing the rabbit to inhale 100% hydrogen gas (500 mL/min) with room air for 30 to 40 s. The decay curve, derived from a UH meter (Unique Medical Co., Tokyo), was recorded on an A/D converter (DR-F1, TEAC Corporation, Tokyo), then processed as a logarithm with a computer (PC-9801, NEC Corporation, Tokyo) to obtain the half-decay time. The absolute rate of blood flow was derived from the half-decay time using the principles and methods of Kety and Schmidt (1948).

According to our previously described method (Hatta et al., 1993; Takahashi et al., 1995), we used an epoxy resin-insulated platinum needle microelectrode of 100 μm in diameter, which was inserted into a 27 gauge (G) needle, for measuring the hydrogen concentration. The active electrode was covered with a vinyl tube except for the tip, the length of which was 700 μm , equivalent to the insertion depth (Figs. 2 and 3). The microelectrode was inserted again into an 18 G needle and inserted through the anterior sclera into the lamellar portion of the optic nerve head carefully, through a contact lens of 60 diopters (Nippon Contact Lens Ins., Nagoya, Japan) under an operation microscope (Carl Zeiss Co., Tokyo) (Fig. 3). A silver-silver chloride wire was implanted under the skin of the back as a reference electrode (Fig. 2).

The anterior chamber was cannulated with a 21 G needle, which was connected to a reservoir filled with artificial aqueous equivalent (Opeguard-MA, Senju Pharmaceutical Company, Osaka, Japan). By controlling the height of the reservoir (Fig. 3), the intraocular pressure (IOP) level was maintained at 15 mmHg, which

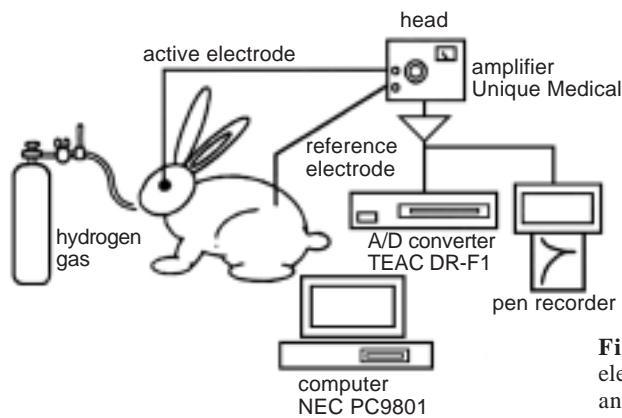


Fig. 2. Block diagram of the measurement of blood flow with hydrogen gas in the optic nerve head.

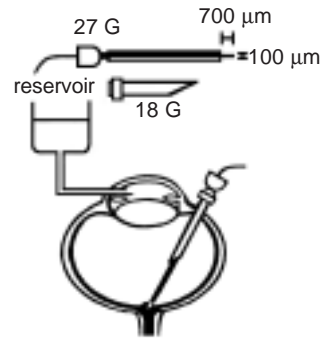


Fig. 3. Schematic diagram of the micro-electrode for measuring hydrogen concentration and its insertion method. The IOP level was maintained at 15 mmHg by controlling the height of the reservoir. The electrode was contrived to set the insertion depth at 700 μm .

is regarded as normal in man and rabbit (Hatta et al., 1993; Takahashi et al., 1995), throughout the experiment.

Each rabbit in the BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups (6 eyes out of 6 rabbits in each group) received the respective dose of BV dissolved in physiological saline solution (1 mL/kg) through the auricular vein over about 1 min. The control group (6 eyes out of 6 rabbits) was given only the saline solution (1 mL/kg). The blood flow in the optic nerve head was measured before and immediately after the drug injection, then at intervals of 10 min. The measurements were made on the left eye of each rabbit in the 3 groups as illustrated in Fig. 2.

The rabbit was killed by an intracardial injection of pentobarbital sodium (about 50 mg/kg) at the end of the experiment. The eyeball was removed and histological examination was made using a light microscope (Olympus Optical Co., Tokyo) to confirm the position of the electrode and tissue damage.

Statistics

All values were expressed as mean \pm SE. Statistical analysis (Wilcoxon's signed-ranks test) was made between each data after the drug administration and the data before the administration. For multiple comparison, an analysis of

variance (ANOVA, Kruskal-Wallis test) and a nonparametric analysis (Dunnett's multiple comparison procedure) were carried out among multiple groups. Values of $P < 0.05$ were considered statistically significant.

Results

Blood flow in the optic nerve head and mean blood pressure in the femoral artery before drug administration

The mean value of the blood flow in the optic nerve head (from the surface of the optic nerve head to 700 μm depth) before drug administration was 110.5 ± 13.4 mL/min/100 g (SE) in the physiological saline solution (1 mL/kg)-administered, control group, 128.1 ± 13.4 mL/min/100 g in the BV (0.1 mg/kg)-administered group and 109.1 ± 8.6 mL/min/100 g in the BV (0.5 mg/kg)-administered group at the normal IOP level of 15 mmHg. There was no significant difference in each mean value of the optic nerve head blood flow among the 3 groups (6 eyes out of 6 rabbits in each group) according to the Kruskal-Wallis test (Table 1).

The mean value of mean blood pressure in the femoral artery before drug administration was 90.3 ± 6.3 mmHg in the control group, 98.5 ± 3.7 mmHg in the BV (0.1 mg/kg)-administered

Table 1. Blood flow in the optic nerve head and mean blood pressure in the femoral artery before drug administration in the control, BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups

	Control group*	BV (0.1 mg/kg)-administered group	BV (0.5 mg/kg)-administered group	Kruskal-Wallis test
Blood flow in the optic nerve head (mL/min/100 g)	110.5 ± 13.4 [6]	128.1 ± 13.4 [6]	109.1 ± 8.8 [6]	NS
Mean blood pressure in the femoral artery (mmHg)	90.3 ± 6.3 [6]	98.5 ± 3.7 [6]	101.2 ± 1.5 [6]	NS

* The control group was given only physiological saline solution (1 mL/kg). Values are expressed as mean ± SE. [], number of animals (eyes) examined. BV, brovincamine fumarate; NS, not significant ($P > 0.05$).

group and 101.2 ± 1.5 mmHg in the BV (0.5 mg/kg)-administered group. There was no significant difference in each mean value of the mean femoral blood pressure among the 3 groups (6 rabbits in each group) (Table 1).

Changes in blood flow in the optic nerve head and in mean blood pressure in the femoral artery throughout the experiment

In the control group (Fig. 4), no significant changes were observed in either the mean value of the blood flow in the optic nerve head or the mean value of the mean blood pressure in the femoral artery after administration of physiological saline solution (1 mL/kg), compared with each corresponding data before administration, which was estimated at 100% at the initial time in the present study, throughout the time course by Wilcoxon's signed-ranks test.

In the BV (0.1 mg/kg)-administered group (Fig. 5), the mean value of the blood flow in the optic nerve head showed a gradual increase immediately after injection and reached the maximal value of 156.5 ± 13.2 mL/min/100 g corresponding to $124.2 \pm 7.3\%$ against the value before injection, at 20 min after injection, followed by a gradual decrease in the blood flow. Statistical analysis showed a significant increase ($P < 0.05$) in blood flow at 10 to 40 min after injection, compared with the initial value before injection according to Wilcoxon's signed-ranks test, but no significant changes were observed in

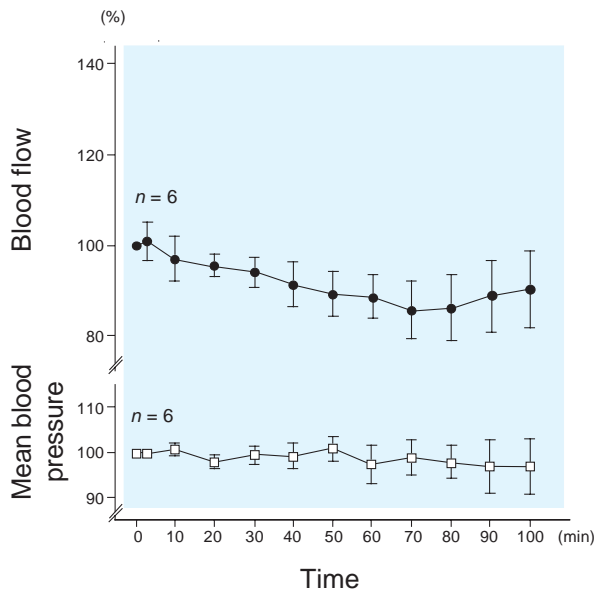


Fig. 4. Changes in blood flow in the optic nerve head and in the mean blood pressure in the femoral artery in the physiological saline solution (1 mL/kg)-administered, control group. Vertical bars indicate SE of the mean; n , number of animals (eyes) examined. No significant changes are observed in either the mean value of the optic nerve head blood flow or the mean value of the mean femoral blood pressure, compared with each corresponding data before administration, which was estimated at 100% at the initial time (0), according to Wilcoxon's signed-ranks test ($P > 0.05$).

the mean value of mean blood pressure in the femoral artery throughout the experiment.

In the BV (0.5 mg/kg)-administered group (Fig. 6), no significant changes were observed in either the mean value of the blood flow in the optic nerve head or the mean value of mean blood pressure in the femoral artery after injection, compared with each corresponding data before injection throughout the time course according to Wilcoxon's signed-ranks test.

An analysis of variance made with the Kruskal-Wallis test showed significant *P* values at 10 to 40 min after drug administration (0.0233 at 10 min, 0.0034 at 20 min, 0.0189 at 30 min and 0.0278 at 40 min) in the comparison of blood flow changes in the optic nerve head in the control, BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups (Table 2). In the multiple comparison of the blood flow in the optic nerve head at 10, 20, 30 and 40 min after drug administration in the 3 groups, Dunnett's multiple comparison procedure showed significant increases in optic nerve head blood flow at 20 to 40 min after injection (*P* < 0.01 at 20 min, *P* < 0.05 at 30 min and *P* < 0.05 at 40 min) in the BV (0.1 mg/kg)-administered group, compared with the corresponding data in the control group (Table 3).

Fig. 6. Changes in blood flow in the optic nerve head and in the mean blood pressure in the femoral artery in the brovincamine fumarate (0.5 mg/kg)-administered group. Vertical bars indicate SE of the mean; *n*, number of animals (eyes) examined. No significant changes are observed in either the mean value of the optic nerve head blood flow or the mean value of the mean femoral blood pressure, compared with each corresponding data before administration, which was estimated at 100% at the initial time (0), by Wilcoxon's signed-ranks test (*P* > 0.05).

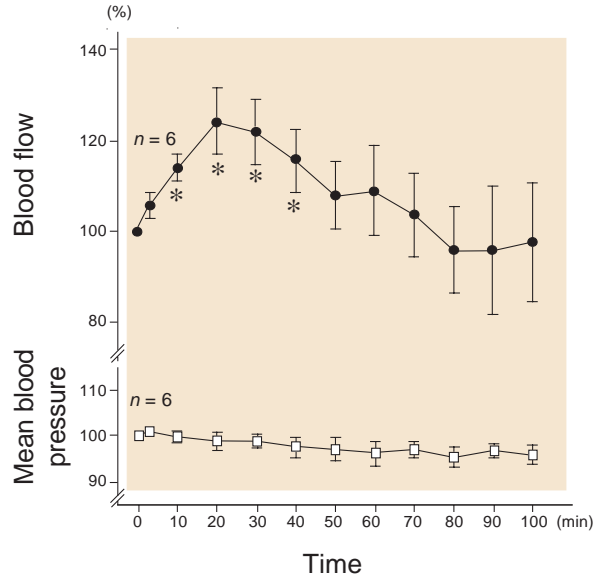


Fig. 5. Changes in blood flow in the optic nerve head and in the mean blood pressure in the femoral artery in the brovincamine fumarate (0.1 mg/kg)-administered group. Vertical bars indicate SE of the mean; *n*, number of animals (eyes) examined. Statistical analysis shows a significant increase in the mean value of the optic nerve head blood flow at 10 to 40 min after injection [*P* < 0.05 compared with the corresponding data before administration, which was estimated at 100% at the initial time (0), according to Wilcoxon's signed-ranks test]. No significant changes are observed in the mean value of the mean femoral blood pressure throughout the experiment.

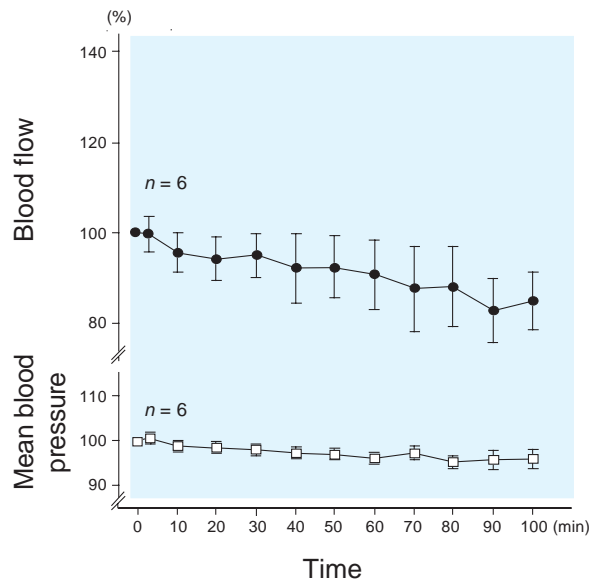


Table 2. Comparison of blood flow changes in the optic nerve head after drug administration in the control, BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups (Kruskal-Wallis test)

	Time (min)										
	Immediately after	10	20	30	40	50	60	70	80	90	100
<i>P</i> value	NS	0.0233	0.0034	0.0189	0.0278	NS	NS	NS	NS	NS	NS

Group given no BV served as the control.

BV, brovincamine fumarate; NS, not significant ($P > 0.05$) (number of eyes examined: 6 eyes in each group).

Changes in the pulse rate, respiratory rate and rectal temperature before and after drug administration

Statistical analyses carried out by the Kruskal-Wallis test and Wilcoxon’s signed-ranks test showed no significant changes in the mean values of the pulse rate, respiratory rate or rectal temperature in any group through the experiment (Table 4).

Histological findings

It was confirmed by the light microscope that the position of the microelectrode for measuring the hydrogen concentration was almost at the center of the optic nerve head. No remarkable tissue damage or hemorrhage was observed due to the fine 100 µm microelectrode used in this test (Fig. 7).

Discussion

The hydrogen clearance method used in the present study is called the most useful technique in investigating microcirculation (Aukland et al.,

1964; Hatta et al., 1993; Takahashi et al., 1995). In this study, the mean value of blood flow in the lamina portion of the optic nerve head before drug administration was 110.5 ± 13.4 mL/min/100 g in the control group, 128.1 ± 13.4 mL/min/100 g in the BV (0.1 mg/kg)-administered group and 109.1 ± 8.6 mL/min/100 g in the BV (0.5 mg/kg)-administered group at the normal IOP level of 15 mmHg. Although variance without statistical significance was observed in each mean value among the 3 groups, these values were almost similar to previously reported mean blood flow rates in the lamina portion of the optic nerve head in normal, adult albino rabbits employing the clearance method at the IOP level of 15 mmHg; 119.3 ± 7.9 mL/min/100 g (Hatta et al., 1993) and 116.6 ± 7.7 mL/min/100 g (Takahashi et al., 1995). These data indicate little difference in the optic nerve head blood flow among the experimental rabbits with a normal IOP level.

In the present study, BV was administered through the auricular vein in rabbits at dosages of 0.1 mg/kg and 0.5 mg/kg. There have been no reports on pharmacokinetics in plasma in rabbits after intravenous administration of the agent. Thus the lower and the higher doses for

Table 3 . Multiple comparison of blood flow in the optic nerve head at 10, 20, 30 and 40 min after drug administration in the control, BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups (Dunnett’s multiple comparison procedure)

	Control group*			
	10 min	20 min	30 min	40 min
BV (0.1 mg/kg)-administered group	NS	$P < 0.01$	$P < 0.05$	$P < 0.05$
BV (0.5 mg/kg)-administered group	NS	NS	NS	NS

* The control group was given only physiological saline solution (1 mL/kg).

BV, brovincamine fumarate; NS, not significant ($P > 0.05$) (number of eyes examined: 6 eyes in each group).

Table 4. Changes in the pulse rate, respiratory rate and rectal temperature before and after drug administration in the control, BV (0.1 mg/kg)- and BV (0.5 mg/kg)-administered groups

	Before	Immediately after	10 min	20 min	30 min	60 min	100 min
Control group*							
Pulse rate (/min)	255 ± 11	252 ± 10	253 ± 11	252 ± 11	257 ± 11	262 ± 12	274 ± 8
Respiratory rate (/min)	54 ± 8	55 ± 9	52 ± 9	51 ± 9	47 ± 5	51 ± 9	41 ± 6
Rectal temperature (°C)	38.8± 0.6	ND	ND	38.8± 0.6	38.8± 0.6	38.6± 0.6	38.3±0.6
BV (0.1 mg/kg)-administered group							
Pulse rate (/min)	262 ± 7	260 ± 7	259 ± 1	262 ± 12	257 ± 10	254 ± 10	255 ± 10
Respiratory rate (/min)	47 ± 3	46 ± 4	45 ± 4	43 ± 4	43 ± 5	43 ± 5	48 ± 4
Rectal temperature (°C)	38.5± 1.1	ND	ND	38.5± 1.1	38.5± 1.1	38.4± 1.2	39.2± 1.3
BV (0.5 mg/kg)-administered group							
Pulse rate (/min)	268 ± 8	259 ± 7	266 ± 8	267 ± 8	264 ± 6	266 ± 5	268 ± 8
Respiratory rate (/min)	43 ± 3	42 ± 3	42 ± 4	42 ± 3	42 ± 3	39 ± 3	37 ± 3
Rectal temperature (°C)	38.3±0.5	ND	ND	38.1±0.6	38.1±0.6	38.1±0.6	37.7±1.0

* The control group was given only physiological saline solution (1 mL/kg). Values are expressed as mean ± SE (number of animals examined: 6 rabbits in each group). BV, brovincamine fumarate; ND, no available data.

intravenous use in rabbits were determined referring to the minimal single dose for intravenous use in humans (about 0.2 mg/kg); this intravenous single dose was estimated to be



Fig. 7. Light micrograph showing the site of insertion of the microelectrode. An arrow indicates the position (hematoxylin and eosin). Bar = 1 mm.

equivalent to the oral single dose, which reaches maximal plasma concentration in 60 min after oral administration in humans (0.3 mg/kg) (Mayo et al., 1982).

The perfusion pressure of optic nerve head circulation is regarded as the gap between blood pressure and IOP. The mean blood pressure in the femoral artery is adopted as the standard blood pressure in our experiments, although, ideally, the mean blood pressure in the ciliary artery, which is about 16 mmHg lower than that in the femoral artery in rabbits (Bill, 1963), should be employed.

In rabbits, autoregulation, which is defined as an autoregulatory function to maintain blood flow by changing vessel resistance when the perfusion pressure decreases (Ojima, 1989), is weak in the optic nerve head (Hatta et al.,

1993). Thus the blood flow in the laminar portion of the optic nerve head at an IOP level of 15 mmHg seems to positively correlate with the perfusion pressure, according to the rule of Poiseuille (blood flow = perfusion pressure/vessel resistance) (Ojima, 1989).

In our research, no significant changes in the mean value of the mean blood pressure in the femoral artery was observed in any group throughout the experiment, as a result of little influence on the systemic blood pressure upon administration (Sugioka et al., 1982). This indicates no significant changes in the perfusion pressure of the optic nerve head throughout the time course. Accordingly, the significant increase in the mean value of the blood flow in the optic nerve head in the BV (0.1 mg/kg)-administered group may result from the decrease of the vascular resistance, that is, the dilation of feeding vessels around the optic nerve head by this agent.

On the contrary, no significant changes in the blood flow in the optic nerve head were observed in either the BV (0.5 mg/kg)-administered group or the control group given no BV throughout the time course. These results indicate the different efficacy of the two doses to the relaxing action of the feeding vessels.

Tsuji (1986) also reported the different efficacy of two different concentrations of prostaglandin I₂ (PGI₂) to the choroidal blood flow in albino rabbits. That is, PGI₂ was administered to the rabbits intravenously at two concentrations of 0.1 µg/kg and 0.5 µg/kg. In the PGI₂ (0.1 µg/kg)-administered group, the choroidal blood flow increased significantly during the 40 min period after administration, but it decreased significantly for 120 min after administration in the PGI₂ (0.5 µg/kg)-administered group. Based upon the findings, it might be possible to presume that the receptor which is activated at a higher concentration may be different from the receptor activated at a lower concentration and that quite opposite effects may appear in experimentation as a result of different receptor responsiveness to drug concentration (Tsuji, 1986). The other report (Kawai and Ohhashi, 1994) also showed that isocarbacyclin (0.1 nM–10 µM), a stable PGI₂

analogue, produced a dose-dependent relaxation in monkey isolated cerebral arteries; the higher concentration of isocarbacyclin elicited a transient contraction which is probably induced through the activation of thromboxane A₂ receptors. A similar mechanism may act even in the case of BV administration.

Furthermore, BV acts as an inhibitor of platelet aggregation through the cyclic AMP pathway (Yasunaga, 1982), as described above. Accordingly, further studies are needed to elucidate the mechanism of the different efficacy of the two doses in light of the cyclic AMP changes in the arterial smooth muscles induced by BV administration, or in light of the receptor responsiveness to drug concentration, besides the action through the blockade of the slow Ca²⁺-channel (Katsuragi et al., 1984), because there is a regional difference in the BV-induced relaxation of the smooth muscles in the rabbit arteries (Narita et al., 1986).

Concerning oral BV therapy for patients with NTG, the lower dose administration of BV furnishes us with the useful suggestion that its potent vasodilation effects in rabbits should improve the optic nerve head blood flow even when orally administered in humans, helping the nerve maintain its integrity more potentially and resulting in favorable results (Hama et al., 1992; Koseki et al., 1994; Sawada et al., 1996), although the therapeutic value of a higher dose of orally administered BV in eyes with NTG remains to be elucidated clinically.

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