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Delayed administration of ethyl eicosapentate improves local cerebral blood flow and metabolism without affecting infarct volumes in the rat focal ischemic model

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Abstract

The objective of this study was to assess whether delayed administration of ethyl eicosapentate has a favorable effect on cerebral blood flow and metabolism in rats suffering from cerebral infarction. Adult male Sprague–Dawley rats weighing 250–300 g were used. Left middle cerebral artery occlusion was induced for 2 h. After 24-h reperfusion, rats were treated with ethyl eicosapentate (100 mg kg^{-1}; ethyl eicosapentate treated) or saline (saline treated) by gavage, once a day for 4 weeks. After 4 weeks, local cerebral blood flow and local cerebral glucose utilization were measured autoradiographically, and infarction size was measured. In the ischemic side, the local cerebral blood flow and local cerebral glucose utilization values in the parietal cortex and the lateral caudoputamen, which constituted the ischemic core, were equivalent to zero in both groups. The peri-infarcted areas, i.e., the frontal cortex and medial caudoputamen, were significantly higher in the ethyl eicosapentate treated group than the saline treated group. In the non-ischemic side, ethyl eicosapentate treated group had a tendency to improve local cerebral blood flow and local cerebral glucose utilization values in a medial caudoputamen. These results suggest that ethyl eicosapentate treatment may be beneficial for maintaining cerebral circulation and metabolism except for infarction area after cerebral infarction.

Keywords: Eicosapentate; Middle cerebral artery occlusion; Cerebral blood flow, local; Cerebral glucose utilization, local; Peri-infarcted area

1. Introduction

Dyerberg et al. reported from their epidemiological survey that the mortality due to arteriosclerotic heart disease was much lower among Greenland Eskimos than among Danes (Dyerberg et al., 1975, 1978). Additionally, Bang et al. reported that the lipid and lipoprotein plasma fractions in Eskimos included low levels of cholesterol, triglycerides, low-density lipoproteins, and very low-density lipoproteins (Bang et al., 1971; Bang and Dyerberg, 1972). They concluded the Eskimo's diet, which was rich in fish containing eicosapentaenoic acid, was responsible. These reports were the first to show an anti-thrombotic action of eicosapentaenoic acid.

Investigations on the anti-thrombotic mechanism of eicosapentaenoic acid have suggested a variety of effects, including: amelioration of hyperlipidemia (Van Gent et al., 1979; Terano et al., 1983), inhibition of platelet aggregation (Dyerberg et al., 1978; Siess et al., 1980; Terano et al., 1983), facilitation of prostacyclin I_3 formation within the vascular wall (Fisher and Weber, 1984), inhibition of thromboxane A_2 and stimulation of thromboxane A_3 formation (Needleman et al., 1979; Dyerberg, 1982), reduction of blood viscosity (Kobayashi et al., 1985), and reduction of blood pressure (Lorenz et al., 1983; Singer et al., 1983). Moreover, we have reported that the long-term administration of ethyl eicosapentate (100 mg kg^{-1} day^{-1}) ameliorated an age-related reduction of local cerebral blood flow and tended to increase local cerebral glucose utilization in stroke-prone spontaneously hypertensive rats (Katayama et al., 1997). As for its effect against brain

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ischemia, it has been reported previously that pre-treatment with eicosapentaenoic acid contributed to reduce brain edema and to improve cerebral metabolism in a rat model for cerebral ischemia (Black et al., 1984a,b; Kashiwagi et al., 1990). However, the question whether delayed administration of eicosapentaenoic acid after ischemia has a favorable effect, has not been demonstrated. Many therapeutic drugs show some efficacy when they are administered either before or within several hours of ischemia. But considering that most stroke patients do not reach medical attention within several hours after the onset of symptoms (Alberts et al., 1990), it would be reasonable to study the effect of delayed treatment.

The objective of this study is to measure local cerebral blood flow and local cerebral glucose utilization when administered ethyl eicosapentate for a long time after middle cerebral artery occlusion, and is to address the question whether delayed administration has a favorable effect on cerebral blood flow and metabolism in a post-infarcted condition.

2. Materials and methods

2.1. Surgical procedure

This experiment was conducted in accordance with the Guidelines for Animal Experimentation of the Nippon Medical School. Eight-week old, male, Sprague–Dawley rats (Hoshino Experimental Animals) weighing approximately 250 g, were used. After 24-h fasting, anesthesia was induced with 2% halothane in a gas mixture of 70% N_2O and 30% O_2, and then maintained with 1% halothane. The animals were placed on a heating pad and rectal and scalp temperatures were maintained between 37.0 and 38.0°C during surgery. A cannula (PE_{50}) for blood pressure measurement and blood collection was inserted into the caudal artery. A median incision was made and the bifurcation of the left common carotid artery was exposed. Caution was taken not to damage the vagal nerve. Both the common carotid and external arteries were ligated with a silk thread.

The middle cerebral artery was occluded for 2 h using an embolization method. A silicone rubber cylinder with tip attached to a 4–0 nylon surgical suture (tip diameter, 0.2–0.3 mm; the nylon surgical thread measured 20 mm with a silicon-coating of 5 mm), was passed through the left internal carotid artery up to the bifurcation of middle cerebral artery. The incision site was sutured, and anesthesia was stopped. After 2-h middle cerebral artery occlusion, animals were anesthetized again with 1% halothane and the surgical thread was removed to allow reperfusion. The animal was allowed free access to food and water during reperfusion.

Arterial blood pressure was monitored continuously for 30 min, from 10 min prior to 20 min after middle cerebral artery occlusion. Blood gases (p_{O_2}, p_{CO_2}, pH) and glucose levels were measured at 10 min before and at 20 min after ischemia.

2.2. Drug administration

Rats were randomly allocated to two groups (ethyl eicosapentate treated and saline treated) 24 h after reperfusion. Each treatment group was divided into three subgroups for the determination of cerebral blood flow ($n = 5$), cerebral glucose utilization ($n = 5$), and infarction size ($n = 5$). The ethyl eicosapentate treated group was given a suspension of eicosapentate ethylester (purity 89.9% Mochida Pharmaceutical) by gavage at a dose of 100 mg kg^{-1} day^{-1} for 4 weeks. The saline-treated group received the same volume of physiological saline by gavage for 4 weeks. These treatments were administered in a blinded fashion.

2.3. Infarction size

To determine the size of infarction, 4% formaldehyde in 0.1 M phosphate buffer (pH 7.4) was infused through the heart in anesthetized rats (2% halothane). The brain was then removed from the skull, cut into in 6 μm sections, and stained with hematoxylin and eosin. The infarction size was measured using an image-analyzer [Microcomputer Imaging Device (MCID system) Imaging Research] for four coronal sections: bregma +1, −1, −3, and −5 mm. Each section was identified by referring to 'The Rat Brain in Stereotaxic Coordinates' (Paxinos and Watson, 1986). The infarction area and the total area of the coronal section were measured; the infarction size was expressed as the percent of infarct area/total area of the coronal section.

2.4. Measurements of local cerebral blood flow and local cerebral glucose utilization

The local cerebral blood flow was determined according to the method of Sakurada et al. (Sakurada et al., 1978) using [^{14}C]iodoantipyrine (American Radiolabeled Chemicals). Animals were anesthetized with 2% halothane 2–3 h prior to local cerebral blood flow measurement, a cannula (PE_{50}) was inserted into the femoral artery and vein, and anesthesia was immediately discontinued. [^{14}C]Iodoantipyrine (150 μCi kg^{-1} dissolved in physiological saline), was infused into the femoral vein for 30 s, and arterial samples were collected every 3 s. The animals were decapitated immediately after cessation of infusion, brains were removed, and placed in isopentane cooled in liquid nitrogen (−50°C). Each brain was then cut into 20 μm coronal

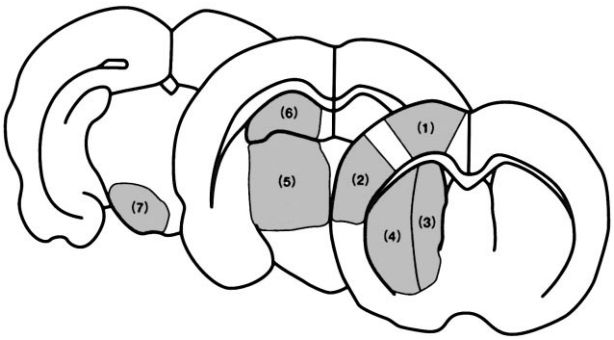

Fig. 1. Anatomic regions of coronal section at level of bregma +1, −3, and −5 mm of rats for autoradiograms. The gray areas represent the regions of interest (ROI). (1) Frontal cortex, (2) parietal cortex, (3) medial caudoputamen, (4) lateral caudoputamen, (5) thalamus, (6) hippocampus, (7) substantia nigra.

sections using a cryostat (−20°C). The sections were placed in contact with X-ray film (Kodak) for 2 weeks along with a [^{14}C]standard (Amersham) for autoradiography. The local cerebral blood flow was calculated from radioactivity levels of [^{14}C]iodoantipyrine in the blood, determined using a liquid scintillation counter, and in the brain tissue, determined by computer-based image analyzer (MCID system).

The local cerebral glucose utilization was determined according to the method of Sokoloff et al. (1977) using [^{14}C]deoxyglucose. After cannulation of the femoral artery and vein under halothane anesthesia, [^{14}C]deoxyglucose (150 μCi kg^{-1}, American Radiolabeled Chemicals) was infused into the femoral vein and arterial blood samples were withdrawn at 15 and 30 s, and at 1, 2, 3, 5, 7, 10, 15, 20, 30, and 45 min after the initiation of infusion. The animals were decapitated 45 min after the initial [^{14}C]deoxyglucose administration. The brain was removed, frozen, and sliced as described for the determination of local cerebral blood flow. The autoradiograms were prepared and the local cerebral glucose utilization was calculated from blood glucose levels, tissue [^{14}C]deoxyglucose and blood [^{14}C]deoxyglucose using the MCID system. These measurements of local cerebral blood flow, local cerebral glucose utilization and infarction sizes were in a blinded fashion.

The regions of interest for measurement of local cerebral blood flow and local cerebral glucose utilization were shown in Fig. 1. The regions of interest was determined in each of the following areas: parietal cortex, lateral caudoputamen, frontal cortex, and medial caudoputamen (bregma +1 mm); thalamus and hippocampus (bregma −3 mm); and substantia nigra (bregma −5 mm). Each anatomical area was identified by referring to 'The Rat Brain in Stereotaxic Coordinates' (Paxinos and Watson, 1986).

2.5. Statistical analysis

All data were expressed as mean ± S.D. Statistical significance of the physiological parameters was analyzed by One-way analysis of variance (ANOVA), local cerebral blood flow, local cerebral glucose utilization, and infarction size between the eicosapentate treated and saline treated groups were analyzed by unpaired *t*-test. The level of significance was set at $P < 0.05$.

3. Results

3.1. Physiological parameters

Table 1 shows the data for the physiological parameters. There were no significant differences in the physiological parameters (rectal temperature, scalp temperature, mean blood pressure, blood glucose, p_{CO_2}, p_{O_2}, and pH) between the two treatment groups before or after ischemia. Additionally, there were no significant differences within either of the two groups before and after ischemia.

Table 1
Physiological parameters

	Ethyl eicosapentate treated group		Saline treated group	
	Before ischemia ($n = 15$)	After ischemia ($n = 15$)	Before ischemia ($n = 15$)	After ischemia ($n = 15$)
Body temperature (°C)	37.3 ± 0.3	37.2 ± 0.3	37.2 ± 0.3	37.3 ± 0.3
Scalp temperature (°C)	37.4 ± 0.2	37.5 ± 0.2	37.5 ± 0.2	37.6 ± 0.3
Blood pressure (mmHg)	96 ± 8	96 ± 9	96 ± 9	97 ± 9
p_{CO_2} (mmHg)	38.6 ± 4.4	38.8 ± 4.7	40.1 ± 2.7	40.3 ± 4.1
p_{O_2} (mmHg)	112 ± 18	106 ± 15	111 ± 21	107 ± 19
pH	7.40 ± 0.03	7.38 ± 0.04	7.39 ± 0.02	7.38 ± 0.03
Blood glucose (mg dl^{-1})	108 ± 17	110 ± 19	108 ± 19	108 ± 19

Values are the mean ± S.D.
There were no differences between the ethyl eicosapentate treated group and the saline treated group before nor after ischemia.

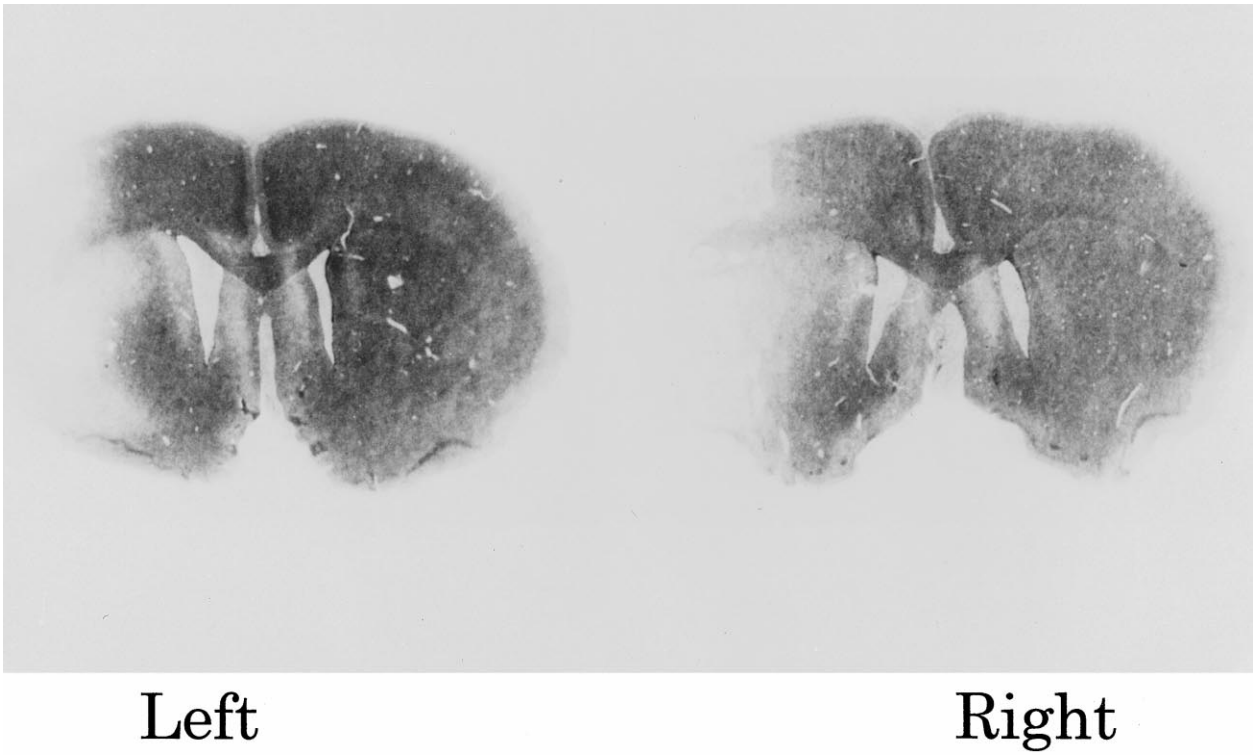

Fig. 2. H-E staining of coronal sections after middle cerebral artery occlusion. The light colored area corresponds to infarcted tissue. There was no significant difference in the size of infarction between the ethyl eicosapentate treated group (left) and the saline treated group (right).

3.2. Measurement of infarction size

In both the ethyl eicosapentate treated and saline treated groups, infarctions were observed in all areas perfused by the middle cerebral artery. The tissues in these areas were shrunken 4 weeks after middle cerebral artery occlusion (Fig. 2). The percent of infarction in the bregma +1 mm section was 15 ± 4% in the ethyl eicosapentate treated

Table 2
Percentage of infarcted area (%)

	Bregma +1 mm		Bregma −1 mm		Bregma −3 mm		Bregma −5 mm	
Ethyl eicosapentate treated group	15 ± 4	N.S.	17 ± 4	N.S.	18 ± 3	N.S.	9 ± 3	N.S.
Saline treated group	15 ± 6	N.S.	17 ± 6	N.S.	18 ± 3	N.S.	7 ± 3	N.S.

Values are the mean ± S.D. and percentage of infarcted area of the coronal section.
N.S.: not significant.

Table 3
Local cerebral blood flow

	Ischemic side		Non-ischemic side	
	Saline treated ($n = 5$)	Ethyl eicosapentate treated ($n = 5$)	Saline treated ($n = 5$)	Ethyl eicosapentate treated ($n = 5$)
Frontal cortex	63 ± 10	89 ± 18[a]	188 ± 15	179 ± 26
Parietal cortex	0	0	175 ± 12	194 ± 30
Medial caudoputamen	55 ± 5	77 ± 18[a]	144 ± 19	171 ± 21
Lateral caudoputamen	0	0	144 ± 12	164 ± 24
Thalamus	90 ± 18	104 ± 22	125 ± 29	139 ± 15
Hippocampus	74 ± 20	73 ± 20	86 ± 16	87 ± 19
Substantia nigra	91 ± 27	97 ± 38	98 ± 24	112 ± 22

Values are the mean ± S.D.
[a] $P < 0.05$, significant difference between the ethyl eicosapentate treated group and the saline treated group.

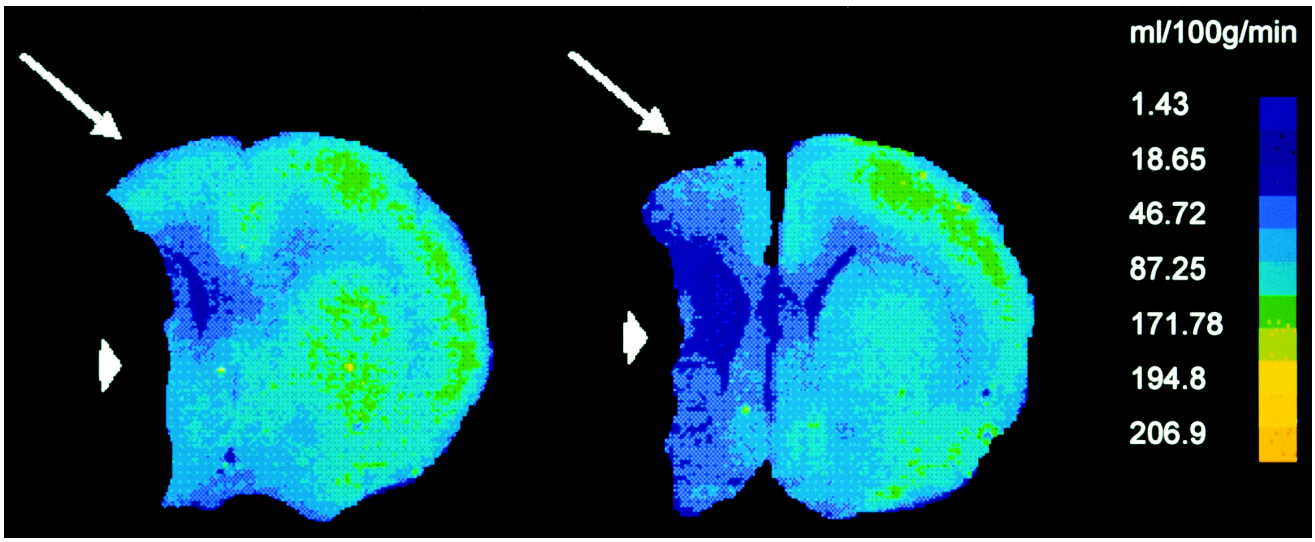

Fig. 3. Autoradiogram using [^{14}C]iodoantipyrine showing local cerebral blood flow 4 weeks after reperfusion following 2-h ischemia in a coronal section at the level of the caudoputamen. Local cerebral blood flow of frontal cortex (↑) and medial caudoputamen (▲) in the ethyl eicosapentate treated group (left) were significantly higher than in the saline treated group (right).

group and 15 ± 6% in the saline-treated group; there was no significant difference between the two treatment groups, in this or any area studied (Table 2).

3.3. Measurement of local cerebral blood flow

The local cerebral blood flow values for each area are listed in Table 3. No ^{14}C could be detected in the regions which constituted the ischemic core, i.e., the parietal cortex and lateral caudoputamen; therefore, the local cerebral blood flow values in these areas was determined to be zero at 4 weeks. The local cerebral blood flow values were significantly higher in the ethyl eicosapentate treated group than in the saline treated group in the frontal cortex (89.4 ± 18.0 vs. 63.4 ± 9.6 ml 100 g^{-1} min^{-1}) and in the medial caudoputamen (76.9 ± 17.7 vs. 55.2 ± 4.6 ml 100 g^{-1} min^{-1}) (Fig. 3). There were no significant differences between the two groups in the other areas measured: thalamus, hippocampus and substantia nigra. In the non-ischemic side, there were no statistical differences in local cerebral blood flow in any area measured between the two treatment groups, but in the ethyl eicosapentate treated group, the local cerebral blood flow tended to be higher in a medial caudoputamen ($P = 0.066$).

3.4. Measurement of local cerebral glucose utilization

The local cerebral glucose utilization values for each area are listed in Table 4. The local cerebral glucose utilization in the parietal cortex and lateral caudoputamen was equivalent to zero in both groups since ^{14}C could not be detected in those regions at 4 weeks reperfusion. The local cerebral glucose utilization values were significantly higher in the ethyl eicosapentate treated group than in the saline treated group, 53.2 ± 3.1 vs. 41.9 ± 5.5 μmol 100 g^{-1} min^{-1} and 56.3 ± 6.5 vs. 44.9 ± 5.3 μmol 100 g^{-1} min^{-1}, in the frontal cortex and the medial caudoputamen, respectively (Fig. 4). No significant differences were found between the two treatment groups in the other areas measured. There were no differences between the two groups

Table 4
Local cerebral glucose utilization

	Ischemic side		Non-ischemic side	
	Saline treated ($n = 5$)	Ethyl eicosapentate treated ($n = 5$)	Saline treated ($n = 5$)	Ethyl eicosapentate treated ($n = 5$)
Frontal cortex	42 ± 6	53 ± 3[a]	86 ± 13	88 ± 9
Parietal cortex	0	0	90 ± 12	88 ± 6
Medial caudoputamen	45 ± 5	56 ± 7[b]	79 ± 10	90 ± 8
Lateral caudoputamen	0	0	81 ± 13	93 ± 11
Thalamus	56 ± 9	63 ± 13	75 ± 11	76 ± 7
Hippocampus	51 ± 11	52 ± 9	57 ± 12	63 ± 13
Substantia nigra	58 ± 13	54 ± 6	66 ± 9	69 ± 10

Values are the mean ± S.D.
[a] $P < 0.01$, [b] $P < 0.05$, significant difference between the ethyl eicosapentate treated group and the saline-treated group.

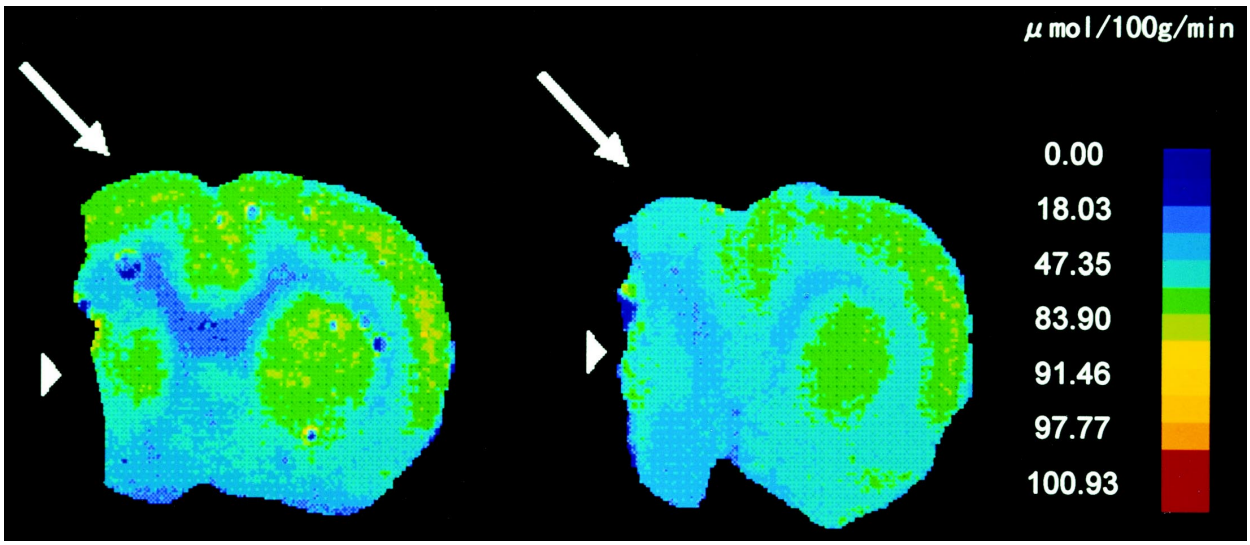

Fig. 4. Autoradiogram using [^{14}C]deoxyglucose showing local cerebral glucose utilization 4 weeks after reperfusion following 2-h ischemia in a coronal section at the level of the caudoputamen. Local cerebral glucose utilization of frontal cortex (↑) and medial caudoputamen (▲) in the ethyl eicosapentate treated group (left) were significantly higher than in the saline treated group (right).

in any area measured on the contralateral side, but in the ethyl eicosapentate treated group, the local cerebral glucose utilization tended to be higher in the medial caudoputamen ($P = 0.074$).

4. Discussion

Since a therapeutic potential for eicosapentaenoic acid was first suggested in the epidemiological studies in North West Greenland (Bang et al., 1971; Bang and Dyerberg, 1972; Dyerberg et al., 1975, 1978), much attention has been paid to its antithrombotic effect. Many studies have been conducted to determine the antithrombotic mechanism of eicosapentaenoic acid (Dyerberg et al., 1975, 1978; Needleman et al., 1976, 1979; Culp et al., 1979; Van Gent et al., 1979; Siess et al., 1980; Dyerberg, 1982; Lorenz et al., 1983; Singer et al., 1983; Terano et al., 1983; Fisher and Weber, 1984; Kobayashi et al., 1985). Many possible mechanisms for the protective effect of eicosapentaenoic acid were found including inhibition of platelet aggregation (Dyerberg et al., 1978; Siess et al., 1980; Terano et al., 1983), vasodilatory action (Needleman et al., 1976, 1979; Dyerberg et al., 1978; Culp et al., 1979), facilitation of red cell deformability (Terano et al., 1983), and reduction of blood viscosity (Kobayashi et al., 1985). In the previous investigation, the effective dose of ethyl eicosapentate on mortality, improving age-dependent reduction of cerebral blood flow and ameliorating brain edema after ischemia was 100 mg kg^{-1} day^{-1} by gavage for a long time (Kashiwagi et al., 1990; Katayama et al., 1997). And then, in the present investigation, we measured local cerebral blood flow and local cerebral glucose utilization after 4 weeks treatment with high purity ethyl eicosapentate at a dose of 100 mg kg^{-1} day^{-1} using rat focal ischemic model.

Recently, several rat models for focal cerebral ischemia have been developed which result in a consistent infarction and in which most physiological parameters are well-controlled (Tamura et al., 1981; Chen et al., 1986; Koizumi et al., 1986; Brint et al., 1988; Nagasawa and Kogure, 1989). Especially the rat model in which the middle cerebral artery is occluded intraluminally using a silicone rubber cylinder attached to a nylon suture via the carotid artery, has the advantage of not requiring a craniotomy, thus, eliminating an invasive surgical procedure, and reperfusion is easily induced (Koizumi et al., 1986). Therefore, it is an appropriate model for testing the efficacy of agents on focal cerebral ischemia.

Rats were treated with ethyl eicosapentate or saline after 24-h reperfusion following 2-h middle cerebral artery occlusion. In the clinical study of the time delay in presentation of stroke patients, most stroke patients did not present within 24 h of symptom onset (Alberts et al., 1990). And then, the treatment was started at this point to investigate whether delayed administration of ethyl eicosapentate has a favorable effect.

There was no difference in infarction size between ethyl eicosapentate treatment group and saline treated group. We studied previously the pathological changes at 24-h reperfusion following 2-h ischemia using this focal ischemic model, and reported that the typical ischemic changes, such as shrunken and triangular neurons, were observed (Katsumata et al., 1995). As a result, irreversible changes were already induced in the middle cerebral artery area at 24-h reperfusion following 2-h ischemia, and this delayed treatment was not effective for decreasing infarction size.

In the ischemic side, the parietal cortex and lateral caudoputamen constituted the ischemic core and were

found to have shrunken 4 weeks following ischemia. The local cerebral blood flow and local cerebral glucose utilization values were equivalent to zero since they could not be distinguished on the autoradiograms from background signals.

In the frontal cortex and medial caudoputamen, the local cerebral blood flow and local cerebral glucose utilization values of the ethyl eicosapentate treatment group were significantly higher compared to the saline treated group. These areas constitute the peri-infarcted area and are located in the watershed area between the anterior cerebral artery and middle cerebral artery. In a report by Dempsey et al. (1985), a reduction of cerebral blood flow and a marked increase in the thromboxane A_2 level were noted in the peri-infarcted area in a cat model for middle cerebral artery occlusion. Other studies have confirmed that thromboxane A_2 levels increased in the peri-infarcted area, where blood flow is somewhat preserved, following ischemia (Gaudet and Levine, 1979; Gaudet et al., 1980). We have previously reported that hypoperfusion in the peri-infarcted area was present at 24 h and 7 days reperfusion following 2 h of ischemia in the same middle cerebral artery occlusion model (Katsumata et al., 1995). Therefore, we can speculate that hypoperfusion, stimulation of platelet aggregation, and an increase in thromboxane A_2 levels probably occurred in the peri-infarcted area in this study.

Eicosapentaenoic acid can be utilized in platelets and the vessel wall to synthesize three-series prostaglandins such as thromboxane A_3 and prostacyclin I_3. Thromboxane A_2 is a potent vasoconstrictor and platelet aggregator. Thromboxane A_3, however, is not a platelet aggregator, and prostacyclin I_3 resembles prostacyclin I_2 in its vasodilator and anti-aggregatory properties (Needleman et al., 1976, 1979; Dyerberg, 1982). Eicosapentaenoic acid is known to reduce thromboxane A_2 production by blood platelets through its competitive inhibition of arachidonic acid metabolism (Needleman et al., 1976, 1979). It is possible that eicosapentaenoic acid improves the local cerebral blood flow in the peri-infarcted area by preventing the rise of thromboxane A_2 levels, thus, reducing the stimulation of platelet aggregation and the constriction of peripheral blood vessels.

On the other hand, in the ethyl eicosapentate treated group the local cerebral blood flow tended to be higher in the medial caudoputamen in the non-ischemic side. These areas are perfused by perforating branches from the anterior cerebral artery and middle cerebral artery. Previously, treatment with ethyl eicosapentate was shown to prevent age-related reduction of cerebral blood flow in the perforating area in stroke-prone spontaneously hypertensive rats (Katayama et al., 1997). This improved circulation of perforating branches may be the result of the mentioned actions of ethyl eicosapentate.

Improvement areas of local cerebral blood flow coincided with that of local cerebral glucose utilization. The most likely mechanism is that more oxygen and glucose are supplied when cerebral blood flow increases. Additionally, other actions of eicosapentaenoic acid, including its rheological properties of erythrocytes (Terano et al., 1983), its vasodilatory action (Needleman et al., 1976, 1979; Dyerberg et al., 1978; Culp et al., 1979), and its reduction of blood viscosity (Kobayashi et al., 1985), would also contribute to the improvement of local cerebral blood flow, further improving the local cerebral glucose utilization.

It has often occurred in the clinical case that an area of decrease in cerebral blood flow on single photon emission tomography (SPECT) is more extensive than a hypodensity area on computerized tomography (CT). In the chronic cerebral infarction, the peripheral area surrounding infarction was characterized by a moderate decrease of cerebral blood flow on SPECT and by a normal density on CT (Raynaud et al., 1987). In an experimental focal ischemic model, prolonged decrease of flow in tissue surrounding infarction could lead to tissue damage (Mies et al., 1983). Moreover, local cerebral blood flow levels were reduced not only in ipsilateral ischemic regions but also in contralateral regions (Bolander et al., 1989; Katsumata et al., 1995). Therefore, the improvement of cerebral blood flow and metabolism in the peri-infarcted areas and contralateral regions that we have presented in this investigation may have important implication to prevent deterioration of infarction.

In this investigation, we did not assess neurological status after ethyl eicosapentate or saline treatment. Previous clinical study was reported that the volume of penumbra was correlated with the neurological status of the patients (Raynaud et al., 1987). Therefore, further study should be necessary to investigate whether treatment with ethyl eicosapentate for a long time after ischemia might improve neurological status.

In conclusion, delayed administration of ethyl eicosapentate after ischemia significantly improved local cerebral blood flow and local cerebral glucose utilization in the peri-infarcted area, and contributed to increase local cerebral blood flow and local cerebral glucose utilization in the contralateral medial caudoputamen. These results suggest that ethyl eicosapentate may have a beneficial effect on cerebral blood flow and metabolism after cerebral infarction.

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