The Effects of Calcium Antagonists on EEG, Evoked Potentials and Neurologic Recovery after Complete Global Brain Ischemia for 15 minutes in Dogs

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The effects of three calcium antagonists on the recovery from neurologic damages after complete global brain ischemia were examined by evaluating the change of a electroencephalogram (EEG), evoked potentials (EP) and a neurologic recovery score (NRS) in dogs. Fifteen minutes global brain ischemia was achieved by occluding the ascending aorta and the caval veins. Nicardipine (NC), flunarizine (FL) and diltiazem (DL) were administered with continuous infusions for three days after the ischemia. The EEG-EP scores (0:no response – 6:normal) 3 hr after the ischemia were 1.4 ± 0.4 (mean ± SE) in the control, 2.2 ± 0.3 in the NC, 2.2 ± 0.4 in the FL and 2.1 ± 0.2 in the DL. There were no significant differences between the 4 groups. The survival rates on the 7th day after the ischemia were 67% (6/9) in the control, 78% (7/9) in the NC, 56% (5/9) in the FL and 89% (8/9) in the DL. No significant differences were presented between the 4 groups. The NRSs (0:death – 100:normal) on the 7th day were 40.3 ± 7.3 in the control, 59.0 ± 8.5 in the NC, 63.2 ± 9.7 in the FL and 55.7 ± 3.3 in the DL. Each treated group showed a tendency to have a higher NRS than that in the untreated control group. The NRS in all dogs treated by the Ca^{++} antagonists on the 7th day was 58.7 ± 4.1, which was significantly higher than that in the control group ($P < 0.05$). We conclude that the continupus administration of calcium antagonists for three days after the global brain ischemia would be beneficial for the neurologic recovery. (Key words: complete global brain ischemia, calcium antagonists, neurologic recovery, EEG, evoked potentials)

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A postischemic hypoperfusion and a delayed neuronal death may contribute to an aggravation of cerebral damage after brain ischemia[1,2]. A rapid increase of intracellular calcium ion (Ca^{++}) during or immediately after brain ischemia has been perceived[3]. The increased Ca^{++} may induce a postischemic hypoperfusion due to cerebral vasospasm and increasing blood viscosity after brain ischemia. A delayed neuronal death may be attributed to an increasing presynaptic release of excitatory amines, such as glutamate. Glutamate augments the influx of Ca^{++} and increases the intracellular Ca^{++} concentration of nerve cells[3]. The excessive increase of intracellular Ca^{++} after brain ischemia aggravates the damage to nerve cells by disturbing intracellular functions through

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several mechanisms[3]. If we can inhibit these reactions, the injury to nerve cells after brain ischemia could be prevented. It has been reported that some calcium antagonists can prevent the postischemic hypoperfusion and improve the neurologic recovery after global brain ischemia in animal experiments[4–6].

We have reported the effect of nicardipine given for 2 hr after the 10 min global brain ischemia in dogs[7,8]. Nicardipine enhanced the neurologic recovery on the 2nd and the 3rd day after the ischemia, but on the 7th day there was no difference between the treated and the untreated group. It is conceivable that a longer period of continuous administration of calcium antagonists might reduce a delayed neuronal death and improve a neurologic recovery after brain ischemia. Therefore, we studied the effects of calcium antagonists administered for three days after the 15 min complete global brain ischemia in dogs.

Materials and Methods

These experiments were approved by the animal cares committee of Tohoku University School of Medicine.

Thirty six mongrel dogs were divided into the 4 groups, 9 in the nicardipine (NC) group (body weight: 9.7 ± 0.5 (mean ± SE) kg, age: 2.3 ± 0.2 years old), 9 in the flunarizine (FL) group (10.5 ± 0.3 kg, 2.4 ± 0.3 years old), 9 in the diltiazem (DL) group (10.0 ± 0.5 kg, 2.0 ± 0.4 years old) and 9 in the control group (10.9 ± 0.5 kg, 1.8 ± 0.2 years old). There were no significant differences in weight and age between the groups.

Anesthesia was induced with 25 $mg \cdot kg^{-1}$ of thiopental sodium and maintained with 0.3% of halothane in oxygen and pancuronium. Each dog was intubated with a cuffed tube and ventilated to maintain a Pa_{CO_2} between 35 and 40 mmHg by an animal ventilator (R-60, Aika). A femoral artery and a forepaw vein were catheterized for blood pressure measurement and administration of drugs. Lactated Ringer's solution was administered with 6 $ml \cdot kg^{-1} \cdot hr^{-1}$ before the ischemia and 8 $ml \cdot kg^{-1} \cdot hr^{-1}$ after the ischemia. The upper esophageal temperature was maintained between 37.0 and 38.0°C before the ischemia. Following left thoracotomy, tapes were placed around the bases of the ascending aorta, and the superior and inferior caval veins respectively. Fifteen minutes of complete global brain ischemia was achieved by occluding the great vessels with these tapes. During the occlusion, the heart was cooled with cold lactated Ringer's solution for myocardial protection. Recirculation was established by releasing the occlusion after drawing up the cold solution, and 10–15 ml of 7% $NaHCO_3$ was administered. Either epinephrine (0.1 mg) or ethylephrine (1 mg)

Table 1. The measuring methods of EEG and evoked potentials

	ABR	MLR	SEP	EEG
Stimulation	a left ear 10Hz, 90dB a click sound	a left ear 5Hz, 90dB a click sound	a left median nerve 5Hz, 4mA an electric current	–
Band Width (Average)	100–3,000Hz (1,024)	5–1,000Hz (512)	5–1,000Hz (512)	0.5–30Hz (–)
Duration	10msec	100msec	100msec	–
Electrodes Position	a vertex(+) a lt ear(–)	same as ABR	a forehead(+) 2 cm lt from a vertex(–) a spinous process(C2)(–)	a vertex(+) a lt ear(–) a forehead(+) 2cm lt from a vertex(–)

Needle electrodes were used to measure EEG and evoked potentials.

Table 2. EEG grade and EEG-EP score

1. Classification of EEG findings (EEG Grade)
   - Grade 1 dominant, normal alpha-activity with theta-delta-activity
   - Grade 2 dominant theta-delta-activity with detectable normal alpha-activity
   - Grade 3 theta-delta-activity without alpha-activity
   - Grade 4 low voltage delta-activity or monophonic, non-reactive alpha-beta-activity possibly with short isoelectric intervals
   - Grade 5 very flat to isoelectric EEG
2. Score of EEG and EP findings (EEG-EP Score)
   1) Score of EEG 2:Grade 1, 1:Grade 2 or 3, 0:Grade 4 or 5
   2) Score of EP
      a) ABR 5 wave 1:recognized, 0:not recognized
      b) MLR Pa wave 1:recognized, 0:not recognized
      c) SEP N2 wave 1:recognized, 0:not recognized
      d) SEP N3 wave 1:recognized, 0:not recognized

   Total of the above
   (6:normal – 0:serious deterioration of electric brain function)
   ABR 5 wave:the 5th positive wave of ABR, MLR Pa wave:the second large positive wave of MLR, SEP N2 wave:the second negative wave of SEP, SEP N3 wave:the third negative large wave of SEP.

was injected for raising blood pressure, if necessary.

One of three calcium antagonists was administered randomly intravenously in bolus immediately after recirculation followed by continuous infusion for 3 days with the following doses; NC with 10 $\mu g \cdot kg^{-1}$ in bolus iv and 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of continuous infusion, FL with 200 $\mu g \cdot kg^{-1}$ and 6.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, DL with 50 $\mu g \cdot kg^{-1}$ and 0.83 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The control group was received no calcium antagonist. Blood pressure, heart rate, esophageal temperature, hematocrit, blood glucose concentration, blood lactate concentration, arterial blood gases, a electroencephalogram (EEG) and evoked potentials (EP) (Neuropack 2, Nihonkohden) were measured before the ischemia, 3 hr and 7 days after the ischemia. The EP applied in this study were an auditory brainstem response (ABR), a middle latency response (MLR) and a somatosensory evoked potential (SEP). The measuring methods of EEG and EP are shown in table 1.

The changes in EEG and EP were evaluated by the score as shown in table 2. The EEG grade was made with reference to that of Hockaday et al[9]. The EEG-EP score which we originated is based on the EEG grade and the appearance of EP waves[10].

Three hours after the ischemia, the chest wall was closed and muscle relaxation was reversed by neostigmine. After enough spontaneous breathing was confirmed by the arterial blood gas analysis and the general observation, the dogs were extubated and returned to the animal cages. The neurologic recovery of the dogs was assessed with the neurologic recovery score (NRS) (table 3). The NRS of each dog was counted once a day for 7 days after the ischemia. Half lactated Ringer's solution with 5% glucose (4 $ml \cdot kg^{-1} \cdot hr^{-1}$) was continuously infused intravenously and amikacin (50 $mg \cdot day^{-1}$) was administered intramuscularly for 7 days after the ischemia.

Statistical analysis was performed by the Student t-test, the Wilcoxon u-test and the X^2 test. $P < 0.05$ was assumed to be a significant difference and $P < 0.15$ was considered to have a tendency of difference. Results are

Table 3. Neurologic recovery score (NRS)

Consciousness: 0 – 15
normal=0, clouded=5, stuporous=10, comatose=15
Respiration: 0 – 15
normal=0, slight abnormal=5, severe abnormal=10,
on ventilator=15
Cranial Nerve Response: 0 – 16
pupil size=0–2, light reflex=0–2, corneal reflex=0–2,
eyelid reflex=0–2, eye position=0–2, facial sensation=0–2,
auditory response=0–2, gag reflex=0–2
Motor and Sensory Response: 0 – 6
muscle tone=0–2, pain response=0–2, body position=0–2
Behavior: 0 – 8
cleaning=0–2, feeding=0–2, drinking=0–2, sitting=0–2
Gait: 0 – 20
normal=0, able to walk with a little ataxia=2.5,
able to walk with ataxia and paresis=5,
unable to walk but able to stand=10, unable to stand=15,
absent of purposeful movement=20
NRS = (1-sum of above score / 80) × 100 (0=death – 100=normal)

Table 4. The physiological indices before the ischemia and 3 hr after the ischemia

	Control		Nicardipine		Flunarizine		Diltiazem	
	Pre	3hr	Pre	3hr	Pre	3hr	Pre	3hr
mean BP (mmHg)	125 ± 7	115 ± 3	126 ± 4	115 ± 4	135 ± 5	134* ± 4	119 ± 5	106 ± 6
HR (min^{-1})	186 ± 7	165 ± 5	173 ± 6	173 ± 6	173 ± 11	157 ± 7	170 ± 12	157 ± 7
BT (°C)	37.5 ± 0.1	36.7 ± 0.4	37.5 ± 0.1	36.8 ± 0.3	37.5 ± 0.1	36.7 ± 0.3	37.4 ± 0.1	35.4* ± 0.2
HT (%)	40.5 ± 1.4	46.7 ± 1.3	35.1 ± 1.5	42.8 ± 2.0	42.2 ± 1.7	50.5 ± 1.7	36.4 ± 1.6	41.8 ± 1.8
Glucose ($mg \cdot dl^{-1}$)	123 ± 8	137 ± 11	107 ± 7	150 ± 12	145 ± 12	153 ± 10	114 ± 11	166 ± 14
Lactate ($mM \cdot l^{-1}$)	1.09 ± 0.24	1.53 ± 0.23	0.96 ± 0.24	1.89 ± 0.38	0.88 ± 0.15	1.84 ± 0.14	0.99 ± 0.05	1.53 ± 0.27
Pa_{O_2} (mmHg)	492 ± 9	455 ± 23	508 ± 12	415 ± 24	441 ± 21	364* ± 27	442 ± 30	307** ± 36
Pa_{CO_2} (mmHg)	37.4 ± 0.7	34.9 ± 0.6	37.1 ± 0.7	36.3 ± 0.6	37.4 ± 0.9	37.8** ± 0.4	37.2 ± 0.5	36.8 ± 1.2
BE ($mEq \cdot l^{-1}$)	−1.74 ± 0.44	−0.16 ± 0.63	−1.02 ± 0.38	−2.60** ± 0.38	−0.99 ± 0.43	−3.30** ± 0.88	0.17 ± 0.67	−2.20 ± 0.70

Each data represent mean ± SE. *$P < 0.05$ vs the control, **$P < 0.01$ vs the control

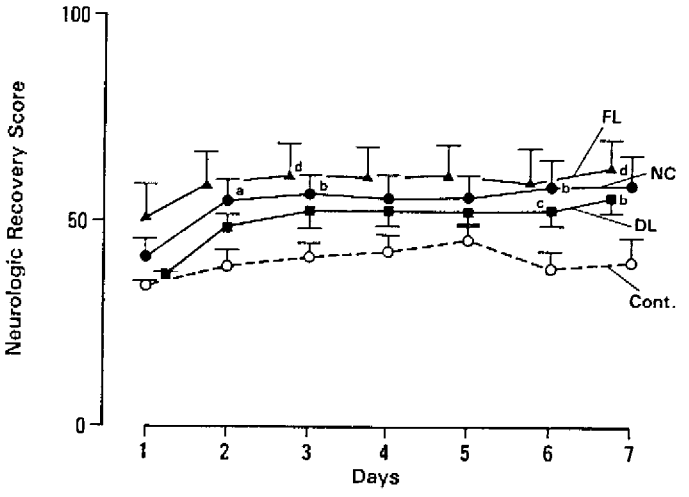

Fig. 1. Each NRS of the 4 groups for 7 days after the brain ischemia.

FL: the flunarizine group, NC: the nicardipine group, DL: the diltiazem group, Cont: the control group. Each point represents the mean ± SE. a: $P < 0.07$ vs the control, b: $P < 0.09$ vs the control, c: $P < 0.10$ vs the control, d: $P < 0.11$ vs the control.

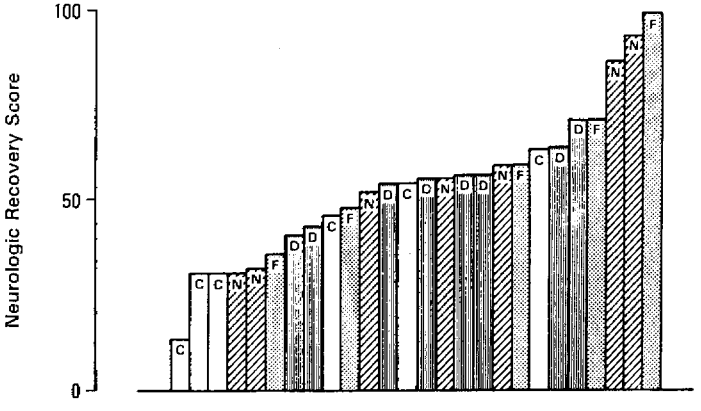

Fig. 2. Each NRS of the all surviving dogs on the 7th day after the ischemia.

F: the dogs of the flunarizine group, N: the dogs of the nicardipine group, D: the dogs of the diltiazem group, C: the dogs of the control group.

expressed as mean ± SE.

Results

The physiological indices before and 3 hr after the ischemia are shown in table 4. There were no significant differences between the control and each of the calcium antagonist group before the ischemia. While, 3 hr after the ischemia, significant differences were presented in mean BP, Pa_{O_2}, Pa_{CO_2} and BE of the FL, in BE of the NC, and in Pa_{O_2} of the DL versus the control.

The survival rates were 67% (6/9) in the control, 78% (7/9) in the NC, 89% (8/9) in the DL and 56% (5/9) in the FL on the 7th day after the ischemia. There were no statistical significances between the groups.

The changes in NRS of the surviving dogs for 7 days are illustrated in figure 1. The NRSs on the 3rd day after the ischemia were 41.4 ± 4.2 in the control, 56.4 ± 5.6 in the NC ($P < 0.09$ vs the control), 61.5 ± 9.8 in the FL ($P < 0.11$ vs the control) and 52.4 ± 3.9 in the DL. The NRSs on the 7th day were 40.3 ± 7.3 in the control, 59.0 ± 8.5 in the NC, 63.2 ± 9.7 in the FL ($P < 0.11$ vs the control), and 55.7 ± 3.3 in the DL ($P < 0.09$ vs the control). The NRS of each surviving dog on the 7th day is shown in figure 2. The dogs with the good recovery (over 70 in the NRS), were observed in the treated group (2 dogs in the NC, 2 dogs in the FL and one dog in the DL). The NRS of all 20 dogs treated with

Table 5. Changes in EEG grade of the 4 groups at 3 hr and on the 7th day after the ischemia

		N	EEG grade 1	2	3	4	5
Cont	3 hr	9	–	–	–	8	1
	7th day	6	–	–	4	2	–
NC	3 hr	9	–	–	1	8	–
	7th day	7	–	3	2	2	–
FL	3 hr	9	–	–	2	7	–
	7th day	5	1	–	4	–	–
DL	3 hr	9	–	–	1	8	–
	7th day	8	–	3	4	1	–

Cont: the control group, NC: the nicardipine group, FL: the flunarizine group, DL: the diltiazem group.

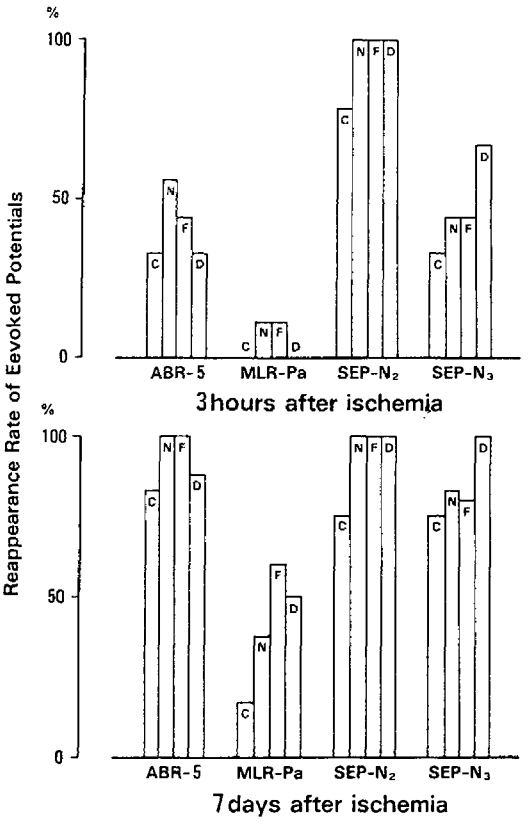

Fig. 3. The reappearance rates of the evoked potentials in the 4 groups at 3 hr and on the 7th day after the ischemia.

ABR-5: the 5th positive wave of ABR, MLR-Pa: the second large positive wave of MLR, SEP-N2: the second negative wave of SEP, SEP-N3: the third negative large wave of SEP, C: the control group, N: the nicardipine group, F: the flunarizine group, D: the diltiazem group.

calcium antagonists on the 7th day was 58.7 ± 4.1, which was significantly higher than that of the control ($P < 0.05$). There were no significant correlations between each NRS on the 7th day and each of the physiological factors at 3 hr after the ischemia in all surviving dogs.

The EEG of Grade 1 and all EP waves were recorded before the ischemia in all dogs. An EEG and all EP waves disappeared during the ischemic period. The first and the third wave of ABR and the N1 wave of SEP reappeared in all dogs at 3 hr after the ischemia. The grades of EEG at 3 hr and on the 7th day after the ischemia are shown in table 5. There were no significant differences in the grade of EEG between the groups.

The reappearance rates of the EP waves at 3 hr and on the 7th day after the ischemia are illustrated in figure 3. The reappearance rates of ABR-5, MLR-Pa and SEP-N3 were low at 3 hr however, these on the 7th day after the ischemia tended to recover. There were no significant differences in the reappearance rates of the EP waves between the groups.

The EEG-EP scores at 3 hr after the ischemia were 1.4 ± 0.4 in the control, 2.2 ± 0.3 in the NC, 2.2 ± 0.4 in the FL and 2.1 ± 0.2 in the DL (fig. 4). On the 7th day, the EEG-EP scores were 2.8 ± 0.5 in the control, 3.8 ± 0.3 in the NC, 4.6 ± 0.3 in the FL ($P < 0.12$ vs the control) and 4.3 ± 0.3 in the DL ($P < 0.14$ vs the control).

Discussion

This study demonstrated that the groups treated with calcium antagonists tended to recover better than the control group in the neurologic recoveries after the complete global brain ischemia. The NRSs of all dogs

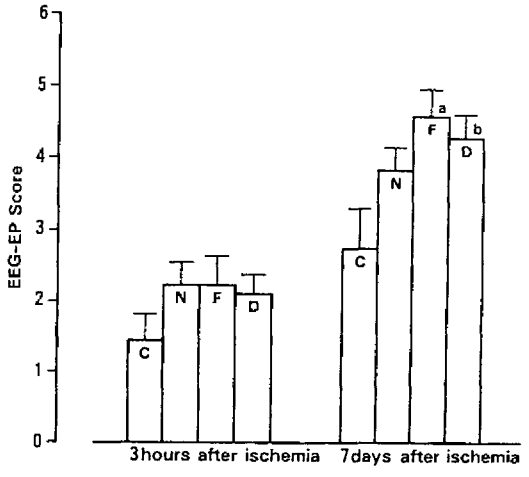

Fig. 4. Changes of EEG-EP score in the 4 groups at 3 hr and on the 7th day after the ischemia.

C: the control group, N: the nicardipine group, F: the flunarizine group, D: the diltiazem group, a: $P < 0.12$ vs the control, b: $P < 0.14$ vs the control.

treated by calcium antagonists were higher than that of the control group on the 7th day after the ischemia, and the good NRSs (over 70) were found only in the treated groups. The EEG-EP scores of the treated groups tended to be higher than that of the control group on the 7th day. However, the EEG grade and the EEG-EP score at 3 hr after the ischemia were not different between the groups. These results suggest that calcium antagonists given after the ischemia have a similar beneficial effect on the neurologic recovery, while they have a little effect on the recovery of electrophysiological functions evaluated by EEG and EP waves at 3 hr after the ischemia.

In our previous study[7], the administration of NC with a dose of 10 $\mu g \cdot kg^{-1}$ in bolus followed 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in continuous infusion prevented the postischemic cerebral hypoperfusion when given after the global brain ischemia. The doses of FL and DL used in this study were reported to increase cerebral blood flow in normal animals[11]. Thus, we selected these doses for this study, expecting an increase in cerebral blood flow after global brain ischemia. These three calcium antagonists used in this study differ slightly each other in their pharmacological properties[12]. However, the recoveries of NRS after the ischemia were not different between the calcium antagonist groups. Therefore, the beneficial effects of these three calcium antagonists may be attributed to the fundamental property of inhibiting the Ca^{++} influx through the calcium channel.

Steen et al.[4] showed nimodipine to improve the neurologic recovery after the complete brain ischemia caused by throttling the neck for 17 min in primates, and Fleischer et al.[6] observed the beneficial effects of lidoflazine in the neurologic recovery after the 10 min complete brain ischemia by occluding the aorta in dogs. However, Vibulstresth[13] reported that nimodipine had no beneficial effects in the pathological recovery after the 20 min forebrain ischemia by the four vessels occlusion in rats. In the randomized clinical study by Forsman et al[14], nimodipine did not improve the neurologic recovery after cardiac arrest. The disagreement of these results may be due to the differences of the extent of ischemic brain damage, of the method of neurologic evaluation and of the drugs used. The extent of damage may depend on the fashion and the duration of brain ischemia and the species of subjects. In our previous study[8], NC given after the 10 min complete brain ischemia by occluding the aorta in dogs improved significantly the neurologic recovery on the 2nd and the 3rd day after the ischemia, but did not influence the neurologic recovery on the 7th day, because the neurologic function of the untreated group recovered spontaneously to the same level as the treated group at the late period (the 6th and the 7th day after the ischemia). In the 15 min complete brain ischemia in this study, NC, FL and DL tended to improve the neurologic recovery on the 6th or the 7th day, because the spontaneous improvement of the neurologic function in the control was small at the late period. According to our studies with the same methods of brain ischemia and neurologic estimation in dogs, calcium antagonists may promote significantly the neurologic recovery

at the early period (the 2nd or the 3rd day after the ischemia) after the moderate cerebral damage (e.g. the 10 min complete brain ischemia), and improve slightly the neurologic recovery in the case of severe brain damage (e.g. the 15 min ischemia).

The excessive increase of intracellular Ca^{++} immediately after ischemia may be induced by: 1) opening of voltage dependent and receptor operated calcium channels, 2) a release from intracellular Ca^{++} regulating organs and 3) a decrease of the efflux through a calcium pump and a Na^{+}-Ca^{++} exchange system[3]. These increased intracellular Ca^{++} may aggravate the damage to nerve cells after ischemia through activations of phospholipases and nucleases, and synthetases of free radicals and thromboxanes etc[3]. A calcium antagonist inhibits a voltage dependent Ca^{++} channel and part of a receptor operated Ca^{++} channel, but may not act on other Ca^{++} pathways[3,15] The development of the delayed neuronal death may be contributed by the increased excitatory amino acids, such as glutamate and aspartate, which increase intracellular Ca^{++} 24 to 48 hr after ischemia. The receptor of excitatory amino acids is separated into two types, an inotropic type and a metabotropic type[15]. An inotropic receptor has three subtypes, a N-methyl-D-aspartate (NMDA) type, a Quisqualate (QA) type and a Kinate (KA) type. Calcium antagonists may inhibit a voltage dependent Ca^{++} influx which is mediated by an influx of Na^{+} and an efflux of K^{+} by activation of QA and KA receptor, but may not inhibit Ca^{++} influx by activation of NMDA and metabotropic receptors[3,15]. Therefore, the effects of calcium antagonists on Ca^{++} regulation and on excitatory amino acids may explain the partial amelioration of these drugs for cerebral resuscitation observed in this study.

In our previous study[16], a thromboxane inhibitor (ONO 3708) administered after the 15 min complete brain ischemia showed a significant beneficial effect on the recovery of the EEG and EP at 3 hr after the ischemia in the same model as this study[16]. Several mechanisms and factors may contribute for the aggravation of brain damages after ischemia. Therefore, the combined use of several drugs, such as thromboxane inhibitors[17], super oxide scavengers[18] and calcium antagonists, might have more beneficial effect on the recovery of nerve cells after ischemia.

The physiological factors, such as body temperature[19], hematocrit and blood glucose[20] have been suggested to influence the neurologic recovery after brain ischemia. The physiological factors before the ischemia were not significantly different between the 4 groups in this study. Three hours after the ischemia, there were significant differences in some factors between the control group and the calcium antagonist groups. However, each NRS on the 7th day after the ischemia did not correlated with each of the physiological factors at 3 hr after the ischemia in all survived dogs. Then, the physiological factors at 3 hr after the ischemia might not affect the NRS within the ranges of each factors in this study.

We conclude that three calcium antagonists, NC, FL and DL, administered continuously for 3 days after the 15 min global brain ischemia would improve similarly the neurologic functions in dogs.

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