Effects of Dopamine on Cortical Blood Flow and Somatosensory Evoked Potentials in the Acute Stages of Cerebral Ischemia

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SUMMARY Effects of intravenous infusion of dopamine on local cortical blood flow (CBF) and somatosensory evoked potentials (SEP) was evaluated using canine cerebral ischemia, which was produced by middle cerebral artery occlusion. CBF was monitored with a H2 clearance method and SEP. P1 to N1 peak to peak amplitude (V1) was recorded by stimulating the sciatic nerve on the contralateral side. CBF and SEP recovered at doses of 5 and 10 \(\gamma\), despite almost no increase of systemic arterial pressure. CBF and SEP were restored at doses of dopamine of 20 and 30 \(\gamma\), with an increase of mean systemic arterial pressure 5 to 15 mm Hg and similar results were obtained at doses of 25 \(\gamma\). Recovery of SEP was slight at extremely high doses of dopamine (65 \(\gamma\)), despite a definite increase of mean systemic arterial pressure (MSAP) and CBF.

IN THE TREATMENT OF THE ACUTE STAGE OF cerebral ischemia, it is of great importance to maintain blood flow, adequate for the recovery of brain function, before irreversible change occurs. However, an agreement has not yet been reached regarding the reasonableness of enhancing decreased blood flow in acute stages of cerebral ischemia because of the possible exacerbation of brain edema.

Dopamine, widely used in the treatment of acute circulatory disorder, is known for its \(\beta\)-action on cerebral and renal arteries causing vasodilatation when used in small amounts, and \(\alpha\)-action causing constriction when used in large amounts. Knowing the relevant effects on cerebralvasodilatation and enhancement of blood flow, dopamine has gradually come into wide use in the treatment of ischemic cerebrovascular disorder. However, only a small number of basic studies have been made concerning the effects of dopamine on cerebral circulation and ischemia.1-3

Methods

Twenty-five mongrel dogs weighing 7-14 kg were examined. They were first anesthetized with intramuscular injections of atropine sulfate 0.05 mg/kg and ketamine hydrochloride 15 mg/kg. Additionally, pentobarbital sodium 5 mg/kg was given as required. The depth of anesthesia was regulated to such a level that the dogs would move their limbs to painful stimuli. Except when hydrogen was inhaled to measure CBF, respiration was natural, and gas analyses were carried out to confirm that \(\text{PaCO}_2\), \(\text{PaO}_2\), and \(\text{pH}\) were within the normal range. Blood gas analyses were made using Blood Microsystem (ABL 2, Copenhagen). In order to measure systemic arterial pressure (SAP) continuously and to gather blood for gas analysis, a catheter was inserted through the femoral artery to the descending aorta in the chest. Through this catheter, SAP was measured with a pressure transducer and continuously recorded.

Oclusion of the middle cerebral artery was done as follows. After extracting the left eye, a 10 mm diameter burr hole was made immediately above the optic canal and the superior orbital fissure, using a micro air drill under the microscope. No. 5-0 silk threads were placed approximately 6-11 mm (8 mm on the average) distal from the origin of the middle cerebral artery in preparation for the arterial occlusion. Then CBF and SEP were recorded prior to the arterial occlusion.

Measurement of CBF and SEP

The hydrogen clearance method was used for the measurement of CBF. Teflon-coated and platinum black treated needle electrodes (0.3 mm diameter, Unique Medical UHE-100, JAPAN) were placed in the cortex of the ecto-sylvian gyrus and silver chloride electrodes were placed in the cervical subcutaneous area as reference electrodes. CBF was measured by \(\text{H}_2\) clearance type tissue rheometer which was interlocked with an X-Y recorder (Ohkura Desktop, JAPAN). About 10% hydrogen gas was inhaled for 1-2 minutes, and absolute values of CBF were calculated by the initial slope method excluding the first one minute. SEP measurements were carried out by applying stimuli to the sciatic nerve using a stimulator (NSE-3) with its readings recorded by a computer (ATAC 250) which was interlocked with electroencephalography (EEG). Stimulation was done by applying stimuli of 0.5 msec duration, with a frequency of 1 Hz, and an intensity of 20 V via bipolar electrodes. Measurement site was at the middle ecto-sylvian gyrus 2 cm frontal to the line connecting bilateral external auditory meatuses and 2 cm lateral from the midline. Unipolar lead was created by placing a disk electrode on the cerebro surface of the site. Reference electrodes were placed at each of the auricles. After confirming that no artifact existed when EEG was monitored, SEP measurements were made. SEP was obtained by averaging 50 responses with an analysis time of 100 msec. P1 to N1 peak to peak amplitude (V1) was used as a parameter representing brain function.

Electrodes for recording CBF were placed as close
J. Measurement of Wood flow and SEP/IDosis of dopamine

FIGURE 1. Protocol in this study. Dose of dopamine was gradually increased as shown in this figure. Administration of dopamine was interrupted after injections of 30 μg, and resumed to reconfirm the effect of dopamine.

Protocol

Figure 1 shows our study protocol. Prior to the occlusion of MCA, measurements of CBF and SEP control values were performed, and similar tests were conducted 10 and 30 minutes after the occlusion respectively. Sixty minutes after the occlusion, dopamine was intravenously injected as shown in figure 1, and the recovery rates of CBF and SEP were recorded. Measurements were performed more than 10 minutes after each administration of dopamine, when blood pressure and pulse rate became stabilized. Administration of dopamine was interrupted after a dose of 30 μg, and was resumed with a dose of 25 μg injection for reconfirming the effect of dopamine, which was then followed by a large dose of 65 μg. Following the last injection, a final measurement was conducted. The total duration of the study was 2.5 hours. During the experiments, PaCO₂, PaO₂ and blood pH were maintained between 30-35 mm Hg, 90-150 mm Hg and approximately 7.4, respectively.

Result

1. Administration of Dopamine and SAP Changes

Figure 2 shows systolic, diastolic and mean systemic arterial pressure

\[ \text{MSAP} = \frac{2 \times \text{diastolic} + \text{systolic}}{3} \]

It was found that MSAP remained almost unchanged at the post-arterial occlusion, and then at doses of 5 and 10 μg dopamine. MSAP increased by 5-15 mm Hg at doses of 20, 30 and 25 μg, and then again at 25 μg, but the increases were not significant when compared with the value obtained 30 minutes after the arterial occlusion.

A significant increase in SAP was observed at the high dose of 65 μg dopamine. It was noted that MSAP increased by 5-15 mm Hg at doses of 20, 30 μg, and then again at 25 μg, but the increases were not significant when compared with the value obtained 30 minutes after the arterial occlusion.

A significant increase in SAP was seen at doses of 25 and 65 μg, respectively, and a significant drop of SAP was recorded at post-65 μg doses. As for diastolic arterial pressure, a significant decrease was observed at the post-30 μg injection (interruption period), and at the post-65 μg administration (discontinued stage). Pulse rate significantly increased at doses of 10, 20 and 30 μg, and at resumed doses of 25 and 65 μg. A tendency toward tachycardia developed after doses of 20 μg dopamine and the state of arrhythmia was seen developing, in some cases, at doses of 30 μg.

2. Restoration of CBF (fig. 3) and SEP (fig. 4) After Dopamine Injection — Compared With the 30 Minutes Post-occlusion Values

Compared with the values recorded prior to the occlusion set at 100%, as seen in figure 3, CBF decreased to 63 ± 4.4% (mean ± SE) and further down to 55 ± 4.0%, after 10 and 30 minutes, respectively. At doses of 5 and 10 μg, CBF increased by 11 and 15% on the average compared to the 30 minutes post-occlusion value, despite a small fluctuation of MSAP during the same period. MSAP went up by 5-15 mm Hg and CBF increased by 17% and 18% at doses of 20 and 30 μg. MSAP increased further at resumed doses of 25 and 65 μg and CBF also increased by 22% and 29%.

Ten minutes after the occlusion, SEP dropped to 57 ± 8.1% of the pre-occlusion 100% value, and further to 52 ± 7.0% 30 minutes after the occlusion (fig. 4).
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At doses of 5 and 10 \( \gamma \), it recovered to 84\% \pm 8.7 and 74\% \pm 11.4, respectively, representing the restoration rate of 62\% and 42\%. Especially at doses of 5 \( \gamma \), SEP significantly recovered from the 30 minutes post-occlusion value, compared with only slight recovery, 11\% on the average, in CBF.

At doses of 20 and 30 \( \gamma \), SEP recovered significantly to 77\% \pm 9.9 and 90\% \pm 13.4 respectively, representing 48\% and 73\% recovery from the 30 minutes post-occlusion value. Following the interruption of dopamine injection, the value again dropped to 62\% \pm 10.4. At resumed doses of 25 and 65 \( \gamma \), SEP rose to the 76\% \pm 11.7 and 74\% \pm 14.7, 46\% and 42\% restoration of the 30 minutes post-occlusion value. However, the restoration of SEP remained relatively low at high doses of 65 \( \gamma \) dopamine despite a large 30\% recovery of CBF.

3. Comparison of CBF (fig. 5) and SEP (fig. 6) Recovery Between Dogs Treated by Dopamine and Control Dogs Without Dopamine Administration

There were no significant differences in body weight, in CBF at the pre-arterial occlusion stage, and in the sites of ligation on MCA confirmed by autopsy, between 8 control dogs and 17 dopamine treated dogs. CBF before the occlusion of MCA was 52.5 \pm 5.7 ml/100 g/min for the control group and 58 \pm 10.1 ml/100 g/min for the treated group.

Thirty minutes after the arterial occlusion, average CBF was 52\% in the control group and 55\% in the treated group, compared with the 100\% pre-occlusion level, representing only a 3\% difference between these two groups (fig. 5). However, at doses of 5 and 10 \( \gamma \).
dopamine, CBF became 12 and 14% higher than those of the control group, respectively, and at doses of 20 and 30 \( \gamma \), 14 and 25% increases over the control group were recorded. Although there existed a tendency of CBF among the treated group to become larger than that of the control group, these increases were not statistically significant.

Average SEP obtained 30 minutes after the occlusion, was 59% in the control group and 52% in the treated group compared with the 100% pre-occlusion level; the increase not being significant (fig. 6).

With doses of 5, 10, 20 and 30 \( \gamma \) dopamine, SEP in the treated group was larger than those obtained in the control group, by 24%, 42%, 148% and 256%, respectively. The rate of increases after the interruption, and at resumed doses of 25 and 65 \( \gamma \) injections, were 158%, 153% and 57%, respectively. Thus, at doses of 20, 30 and 25 \( \gamma \), the recovery of SEP over those obtained in the control group was significant.

4. Summary of SAP, CBF and SEP in Relation to Doses of Dopamine (fig. 7).

CBF and SEP recovered at doses of 5 and 10 \( \gamma \) despite almost no change of mean SAP, with the recovery of SEP being especially remarkable at doses of 5 \( \gamma \) compared with the restoration of CBF. At doses of 20 and 30 \( \gamma \), both SAP and CBF showed a relatively moderate recovery. However, restoration of SEP was remarkable at doses of 30 \( \gamma \).

At 25 \( \gamma \) doses, accompanied by an increase of SAP, CBF and SEP showed a large increase. At 65 \( \gamma \) doses, however, SEP recovered only slightly despite the remarkably significant rise in SAP and CBF.

Discussion

1. Models Studied and Methods of Physiological Assessment of Ischemia

Concerning the definition of ischemic models produced by the occlusion of the canine middle cerebral artery, elaborate reports have already been made.\(^4,5\) In our present tests, CBF dropped by 44-55% on the average from the pre-occlusion levels 250 minutes after the arterial occlusion. The decrease in CBF value was considered to be that of mild to moderate ischemia, equivalent to the CBF decrease recorded 30-50 minutes after the occlusion of MCA, (mean value: 42.3±51.3%, measured by the \( ^{83} \text{Kr} \) \( \beta \) ray internal carotid injection method), as reported by Nakagawa et al;\(^7\) and also to the CBF decrease 60 minutes after the arterial occlusion (36.8% on the average, measured by the \( \text{H}_2 \) clearance method) reported by Ohtsuka, Nakagawa et al.\(^5,6,8\)

The importance of SEP as a parameter of functional evaluation of cerebral ischemia has increasingly been recognized since the publication of Branston's report.\(^9\) Since the authors have at times reported the importance of SEP as a parameter in evaluating the function of cerebral ischemia, no further elaboration on this is made here.

2. Effects of Low Dopamine Doses on CBF and SEP

Studies were made by Niimi et al\(^3\) on 11 cases of ischemic cerebrovascular disorder and 3 cases of degenerative disease using the Argon inhalation. As results of these studies, it was observed that CBF increased significantly by 12% with intravenous injection of 2 \( \mu \text{g/kg/min} \) (2 \( \gamma \)) dopamine, and by about 10% at doses of 1-4 \( \gamma \). Niimi et al\(^3\) surmised that this CBF recovery was attributable to cerebrovascular vasodilation. Kwak et al.\(^10\) carried out dopamine treatment using a small dose (5-16 \( \gamma \)) method without an increase of SAP, and observed clear clinical effects among 11 out of 13 cases of cerebral ischemia caused by cerebral vasospasm.

In our present studies too, at a low dose of 5 and 10 \( \gamma \) dopamine, CBF recovered by average 11 and 15% respectively (fig. 3) compared with the value obtained 30 minutes after the arterial occlusion, thus representing an average 12% and 14% increase over the control group's values, despite a very small change in the mean SAP. The results indicate an enhancement of CBF even by a small quantity of dopamine, insufficient to cause a change in the mean SAP. The CBF increase was accompanied by recovery of SEP by 62% and 42% on the average compared with the 30 minutes...
post-occlusion value (fig. 4) and 24% and 42% restoration over the control group (fig. 6).

Toda et al. assumed the existence of dopamine receptors because of the effect of dopamine on basilar and middle cerebral arterial specimens extracted from dogs were not suppressed by α-blockade by atropine and adenosine. Similar conclusions were reached by Edvinsson et al. through experiments on the middle cerebral artery and the pial arteriole of the cat.

3. Effects of a High Dopamine Dose on CBF and SEP

Ritchie et al. performed experiments to enhance blood pressure by dopamine injection (20-30% increase in mean SAP) on 9 cases of experimental subarachnoid hemorrhage — produced by injecting blood into feline optic chiasmatic cistern with both blood volume expansion and artificial respiration. It was reported that although 7 out of the 9 cases that were treated survived to sacrifice at 20 hrs., all 5 cases in the non-treated control group died beforehand. It was also reported by Haraguchi et al. that by maintaining systolic arterial pressure at 160–200 mm Hg with doses of 10–30 γ dopamine to 12 cases of symptomatic vasospasm which was caused by the rupture of cerebral aneurysm, it proved to be extremely effective or effective in 10 cases, and 2 cases non-effective.

In the present studies, at a relatively high dose of 20 and 30 γ dopamine, systolic arterial pressure increased by 16 mm Hg on the average, mean SAP by average 4 mm Hg and the pulse pressure by 17 mm Hg respectively, compared with the values recorded 30 minutes after the occlusion. The increase in the pulse rate was of significance.

At doses of 20 and 30 γ dopamine administration, CBF recovered by approximately 18% from the 30 minutes post-occlusion level as shown in figure 3, which represented average 14% and 25% increase over the corresponding figures of the control group (fig. 6). As for SEP, its recovery was significant 48% and 73% (fig. 4) and striking 148% and 256% restoration from the control group (fig. 6).

Such a remarkable jump in the restoration rate as 148% and 256% [in SEP (V.) at doses of 20 and 30 γ] over the control values, was considered to have much to do with a fairly large decrease in SEP (V.) of the non-treated group. Generally, SEP (V.) takes a natural course of a slight increase 2 hours after the occlusion of MCA compared with 30 minutes and 1 hour post-occlusion values. Therefore, it remains unexplained why SEP (V.) in the control group did not recover, but rather declined, 2 hours after the arterial occlusion in the current studies.

Recovery of CBF and SEP was also seen at resumed doses of 25 γ dopamine.

At a large dose of 65 γ, compared with the corresponding values obtained 30 minutes after the occlusion, the systolic blood pressure recorded an increase of average 46 mm Hg, the mean SAP an increase of 25 mm Hg and the pulse pressure an increase of 30 mm Hg, respectively, of which all increases were significant.

An increase of CBF at doses of 65 γ was by 30% from the value obtained 30 minutes after the occlusion and by 49% over that of the control group, both being the most conspicuous increases. Despite this, recovery of SEP was 42% from the 30 minutes post-occlusion value and 57% compared with the control group, both being relatively moderate. This relatively moderate restoration rate of SEP at doses of 65 γ, regardless of a considerable increase of CBF, which accompanied an SAP increase, can be attributed to the development of cerebral swelling due to an excessive increase of SAP.

In applying methods which utilize blood pressure enhancement, due consideration should always be given to risks of exacerbation of cerebral edema caused by the SAP increase; for in our present studies, four cases in which bulging of brain tissue was clearly observed through the burr hole, were exempted from our discussion.

4. Clinical Application of Dopamine

Recently many reports have been made concerning clinical application of dopamine to ischemic cerebrovascular lesions, especially vasospasm which developed following aneurysm surgery. As for criteria for using dopamine, however, no concrete agreement has yet been reached.

As discussed above, since dopamine has an effect of vasodilation when administered in a low dose, and a blood pressure enhancing effect when used in a large quantity, methods of mode of dopamine administration should be determined taking into consideration the degree and stage of cerebral ischemia. In other words, although a high dose of 20–30 γ dopamine, an enhancement of CBF which accompanies a rise of SAP can be expected, it sometimes will exacerbate brain edema, thereby necessitating a cautious selection of cases and careful handling of dopamine.

References

Relationship of Somatosensory Evoked Potentials and Cerebral Oxygen Consumption During Hypoxic Hypoxia in Dogs

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SUMMARY The effects of hypoxic hypoxia on cerebral hemodynamics and somatosensory evoked potential (SEP) were studied in 10 pentobarbital anesthetized dogs. Cerebral blood flow (CBF) was measured using the venous outflow technique and cerebral oxygen consumption (CMRO₂) was calculated from the arterio-cerebro-venous oxygen difference times CBF. SEP was evaluated by percutaneous stimulation of an upper extremity nerve and was recorded over the contralateral somatosensory cortex. The latencies of the initial negative wave (N₁), second positive wave (P₂) and the amplitude of the primary complex (P₁N₁) were measured. Animals were breathed sequentially with oxygen concentrations of 21, 10, 6, 5, and 4.5% for five minutes each. Animals were returned to room air breathing when the amplitude of the SEP decreased to < 20% of control and were observed for 30 minutes following reoxygenation. Severe hypoxia (4.5% O₂) increased CBF to 200% of control, decreased CMRO₂ to 45% of control, decreased amplitude and increased latency of SEP. Following reoxygenation, as CMRO₂ increased toward control, latency of SEP decreased and amplitude increased and CBF returned to baseline within 30 min. During hypoxia and reoxygenation, the latencies of N₁ and P₂ and the amplitude of P₁N₁ were correlated with CMRO₂ in individual animals. We conclude that changes in SEP amplitude and latency reflect changes in CMRO₂ despite high CBF during rapidly progressive hypoxic hypoxia and following reoxygenation.

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