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Comparative Effects of Lingual and Facial Nerve Stimulation on Intracranial and Extracranial Vasomotor Responses in Anesthetized Cats

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SATO, M., IZUMI, H., KARITA, K. and IWATSUKI, N. *Comparative Effects of Lingual and Facial Nerve Stimulation on Intracranial and Extracranial Vasomotor Responses in Anesthetized Cats.* Tohoku J. Exp. Med., 1997, **182** (2), 103-113 —— Electrical stimulaion of the central cut end of the lingual nerve (as reflex activation of parasympathetic nerve) or of the peripheral cut end of the facial (VII*th* cranial) nerve (as direct activation of parasympathetic nerve) elicited the ipsilateral blood flow increases in lower lip, palate and common carotid artery (CCA) but not in frontal cerebral cortex in α-chloralose-urethane anesthetized, vagosympathectomized cats. No significant difference, in terms of the vasomotor changes examined, was found between lingual nerve and facial nerve stimulation. The results suggest that there is no somato-parasympathetic reflex vasodilator mechanism serving the frontal cerebral cortex, and that changes in CCA blood flow should not be taken to be indicative of blood flow changes in cerebrocortical blood flow. However, we cannot entirely rule out the possibility of a neurogenic vasodilator influence of the facial pathway, since small blood flow increases in the frontal cerebral cortex were sometimes observed on facial nerve stimulation. ———— parasympathetic reflex vasodilation; cerebrocortical blood flow; common carotid artery; lip blood flow; palate blood flow

Electrical stimulation of the central cut end of the lingual nerve elicits blood flow increases in many extracranial tissues (such as lower lip, submandibular gland and palate) via reflex activation of the parasympathetic vasodilator fibers running in either the VII*th* or IX*th* cranial nerve in the cat (Izumi and Karita 1994, 1995a; Izumi et al. 1995; Karita et al. 1995). However, it still remains questionable whether intracranial blood flow is increased by such lingual nerve stimulation.

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Changes in common carotid artery (CCA) blood flow have been considered to be indicative of changes in intracranial or extracranial blood flow (Goadsby et al. 1984; Lambert et al. 1984; Carrive and Bandler 1991; Kuo et al. 1995). However, we have recently reported that evoked changes in CCA blood flow cannot be regarded as an accurate reflection of changes occurring simultaneously in individual extracranial tissues, at least when examining the effect on the parasympathetic mediated vasodilation of drugs that act directly on receptors in blood vessels or alter the systemic blood pressure level (Izumi et al. 1997a).

We decided to evaluate the relationship between the changes in blood flow in the CCA and those in various intracranial and extracranial tissues when the changes were evoked by lingual and facial nerve stimulation in the cat. To this end, we measured simultaneously the evoked changes in cerebrocortical blood flow (CBF) and in blood flow in lower lip and palate, which are predominantly innervated by facial (cranial VII*th*) and glossopharyngeal (cranial IX*th*) nerves. For this purpose, we used laser Doppler flowmetry, whereas CCA blood flow changes were assessed using an electromagnetic flowmeter.

Materials and Methods

Twenty-five adult cats, unselected as to sex and of 2.5 to 4.0 kg body weight, were initially sedated with ketamine hydrochloride (30 mg/kg, i.m.) and then anesthetized with a mixture of α-chloralose (50 mg/kg, i.v.) and urethane (100 mg/kg, i.v.). These anesthetics were supplemented if and when necessary throughout the experiment. This experiment was reviewed by the Committee on the Ethics of Animal Experiments in the Tohoku University School of Medicine, and carried out according to the Guidelines for Animal Experiments in the Tohoku University School of Medicine, and The Law (No. 105) and Notification (No. 6) of the Government. Local anesthetic (2% lidocaine, 1–2 ml) was always applied to the areas of the skin that were cut. One cephalic vein was cannulated to allow drug injection. The anesthetized animals were intubated, paralyzed by intravenous injection of pancuronium bromide (Mioblock, Organon, Oss, The Netherlands; 0.4 mg/kg initially, supplemented with 0.2 mg/kg per hour after testing the level of anesthesia; see below) and artificially ventilated via the tracheal cannula with a mixture of 50% air $-$50% O_2. The ventilator (Model SN-480-6; Shinano, Tokyo) was set to deliver a tidal volume of 8–12 cm^3/kg at a rate of 20 breaths/min. The end-tidal concentration of CO_2 was determined by means of an infrared analyzer (Capnomac Ultima; Datex Co., Helsinki, Finland). Continuous ventilation in this manner maintained arterial blood pH at 7.4 ± 0.1, $PaCO_2$ at 34.9 ± 4.2 mmHg and PaO_2 at 289.2 ± 32.7 mmHg. Arterial blood was collected from the femoral artery every 1.5 hours or so for the measurement of pH, $PaCO_2$, and PaO_2 via a blood gas analyzer (Model 178; Ciba-Corning, Medfield, MA, USA). Ringer's solution was continuously infused at a rate of approximately 8–10 ml/kg/hr and 8.4% $NaHCO_3$ solution was added, if necessary, to main-

tain the arterial blood pH and base excess at the value given above, as described before (Izumi et al. 1997b). The criteria for maintenance of an adequate depth of anesthesia were the persistence of miotic pupils and the absence of a reflex elevation of heart rate and arterial blood pressure during stimulation of the lingual nerve. If the depth of anesthesia was considered inadequate, additional α-chloralose and urethane (i.e. intermittent doses of 5 mg/kg and 10 mg/kg i.v., respectively) was administered. Rectal temperature was maintained at 37–38°C using a heating pad.

All experiments were performed on anesthetized cats in which non-cranial cardiovascular effects elicited by lingual and facial nerve stimulation were minimized by cutting the vagus nerve in the neck bilaterally. Furthermore, the sympathetic trunks in the neck were cut bilaterally prior to any experimental stimulation to avoid the involvement of the cervical sympathetics in any reflex effects, and to ensure that only parasympathetic effects were involved in the present study. At the end of the experiment, the cat was killed by an overdose (about 150 mg) of sodium pentobarbital.

In the experiments which involved electrical stimulation of either the central cut end of the lingual nerve or the peripheral cut end of the facial nerve, the relevant nerve was sectioned and stimulated separately and unilaterally under a binocular microscope, as shown schematically in Fig. 1. The root of the facial cranial nerve was divided from its origin in the brain stem after an extensive craniotomy. A bipolar silver electrode attached to a stimulator (Model SEN-

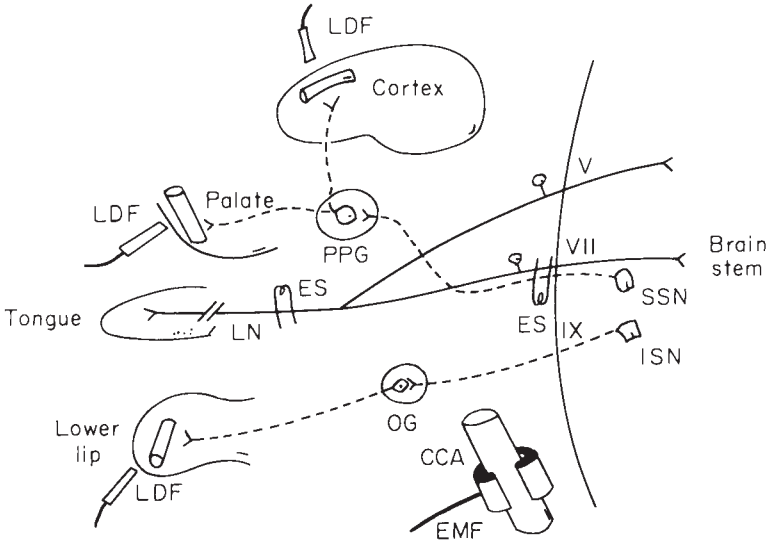

Fig. 1. Schematic representation of the sites of electrical stimulation of lingual nerve and facial nerve root and of blood flow measurement. Afferent pathways are indicated by solid lines, and parasympathetic efferent pathways by broken lines. Abbreviations: CCA, common carotid artery; SSN, superior salivatory nucleus; ISN, inferior salivatory nucleus; LN, lingual nerve; PPG, pterygopalatine ganglion; OG, otic ganglion; V, trigeminal nerve root; VII, facial nerve root; IX, glossopharyngeal nerve root; ES, electrical stimulation; LDF, laser Doppler flowmeter; EMF, electromagnetic flowmeter.

7103; Nihon Kohden, Tokyo) was used for stimulation. The lingual nerve and facial nerve roots were stimulated for 20 seconds using a supramaximal voltage (30 V) at 10 Hz with pulses of 2 msec duration, unless otherwise noted.

After the head of the animal had been fixed in a stereotactic frame (Narishige, Tokyo), changes in blood flow at sites in the palate, the lower lip adjacent to the canine tooth and the frontal cerebral cortex (Fig. 1) were monitored using a laser Doppler flowmeter (LDF, LC-1; Canon, Tokyo or ALF21R; Advance, Tokyo), as described elsewhere (Izumi and Karita 1992b, 1993; Karita and Izumi 1995). To enable measurement of cortical blood flow, a burr hole of 4–5 mm diameter was made in the frontal bone with a dental drill. The exposed dural surface was covered with normal saline. The dura was incised just prior to the taking of blood flow readings. The frontal region was chosen because of the observations that electrical stimulation of either the trigeminal ganglion (Goadsby and MacDonald 1985; Goadsby 1989), dorsal facial area (Kuo et al. 1995), or facial nerve (Goadsby 1991) elicits an increase in regional blood flow in the frontal and parietal areas of the cortex of the cat ipsilateral to the site of stimulation. In those studies, regional tissue blood flow was measured using the radiolabeled-microsphere reference-flow and LDF techniques. Because the LDF system is sensitive to movement in the area in which measurements are being made, the tips of the fiber optic probes were kept at a distance of 0.2–0.5 mm from the surface of the cerebral cortex, lower lip or palate. This was facilitated by their insertion into acrylic dental resin which was attached either to a manipulator fitted onto the stereotactic frame or to the ipsilateral lower incisor. They were positioned without exerting any pressure on the tissues. The present LDF values represent the blood flow in the superficial vessels in each tissue. Electrical calibration for zero blood flow was performed for all recordings. Several gains were selectable and the maximum output of a given gain level (defined electrically) was taken as 100%. The analog output of the equipment does not give absolute values, but shows relative changes in blood flow (for technical details and evaluation of the LDF method, see Stern et al. [1977]).

Blood flow in the CCA was measured using an electromagnetic blood flow transducer fitted to an electromagnetic blood flowmeter (Model MFV-2100; Nihon Kohden, Tokyo), as described before (Izumi et al. 1997a)

Systemic arterial blood pressure was recorded from the femoral catheter via a Statham pressure transducer. A tachograph (Model AT-610G; Nihon Kohden) triggered by the arterial pulse was used to monitor heart rate.

All numerical data are given as the mean $\pm$ S.E.M. The significance of changes in the responses was assessed using an analysis of variance (ANOVA) followed by a Contrast-test and a Mann-Whitney U-test. Differences were considered significant at the level $p<0.05$. Data were analyzed using a Macintosh Computer with StatView 4.5 (Abacus concepts) and Super ANOVA (Abacus concepts).

Results

Average values (±S.E.M.) for mean arterial blood pressure, heart rate and common carotid artery blood flow were 107.3±9.1 mm Hg, 162.6±6.5 beats/min and 10.4±1.5 ml/min, respectively, in our chlorarose-urethane anesthetized, artificially ventilated (50% air −50% O_2), vago-sympathectomized cats.

Effects of lingual nerve stimulation

Fig. 2 shows the effects of electrical stimulation of the central cut end of the lingual nerve at various intensities from 5 to 40 V on blood flow in the ipsilateral lower lip, palate, cerebral cortex and CCA. Averaged data are shown in Fig. 3. Increasing the stimulus voltage above 5–10 V produced progressively bigger blood flow increases in all sites measured, except in the frontal cerebral cortex. The threshold intensity needed to elicit the blood flow increases was 10 V, and all responses were saturated by about 30 V.

Effects of facial (VIIth cranial) *nerve stimulation*

Fig. 4 shows typical examples of the effects of electrical stimulation of the

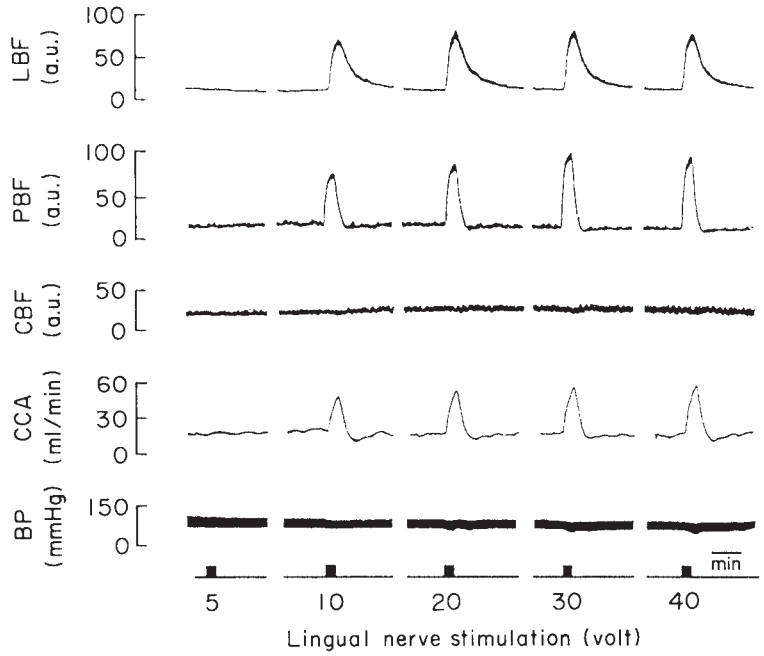

Fig. 2. Intensity-response relationships for evoked changes in blood flow in ipsilateral lower lip (LBF), palate (PBF), cerebral cortex (CBF) and common carotid artery (CCA), as well as in systemic arterial blood pressure (BP), following electrical stimulation of the central cut end of the lingual nerve in vago-sympathectomized cats. Parameters for lingual nerve stimulation (indicated by bars) were 2 msec, 20 Hz for 20 seconds with various intensities (5–40 V). Abscissa, time (minute). Ordinate, lower lip (LBF) and palate blood flow (PBF) in arbitrary units (a.u.), common carotid artery blood flow (CCA) in ml/min and systemic arterial blood pressure (BP, mmHg).

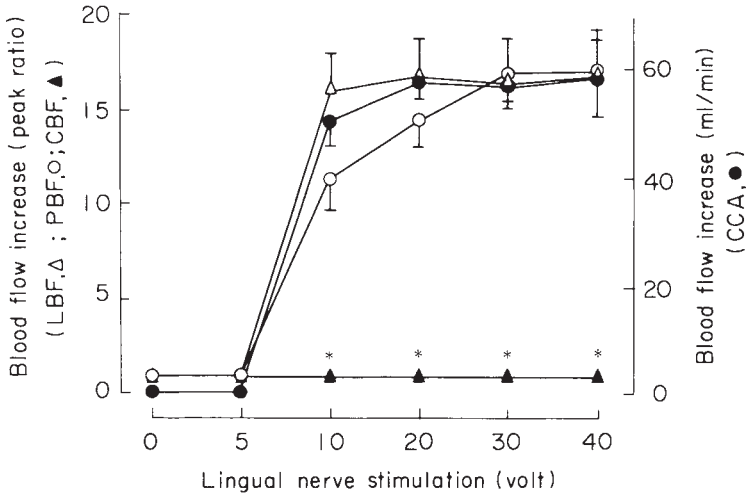

Fig. 3. Averaged data for effects of electrical stimulation of the central cut end of the lingual nerve at various intensities (5–40 V) on blood flow increases in lower lip (LBF, △-△), palate (PBF, ○-○), cerebral cortex (CBF, ▲-▲) and common carotid artery (CCA, ●-●) in vago-sympathectomized cats. Experimental conditions were as in Fig. 2. Blood flow increases in LBF ($n=8$), PBF ($n=8$) and CBF ($n=7$) are each expressed on the ordinate as the ratio of the peak blood flow during the evoked vasodilation to the highest level of the fluctuations in baseline blood flow before lingual nerve stimulation. CCA blood flow increase ($n=7$) is expressed in absolute terms in ml/min. Values shown are means ± S.E.M. Statistical significance was assessed using an analysis of variance (ANOVA) for repeated measurements followed by a contrast test for significance of difference. * $p<0.001$ vs. blood flow response in CCA elicited by lingual nerve stimulation at same intensity.

peripheral cut end of the facial (VII*th* cranial) nerve at various intensities on blood flow in the ipsilateral lower lip, palate, CCA and frontal cerebral cortex of our vago-sympathectomized cats. Averaged data from these experiments are compared with those from the lingual nerve stimulation experiment in Table 1. On the basis of the averaged data, the vasomotor responses in lower lip, palate, CCA and frontal cerebral cortex elicited by facial nerve stimulation were found not to be significantly different from those reflexly elicited by lingual nerve stimulation (Figs. 2 and 3, Table 1). However, a facial nerve-induced increase in CBF was observed in 4 out of 9 animals (Fig. 4), in contrast to the consistent failure of lingual nerve stimulation to elicit a CBF increase. This CBF increase was not a passive effect caused by a concomitant increase in blood pressure, since the latter did not rise (in fact, it tended to fall).

Discussion

Various methods have been utilized for eliciting parasympathetically mediated vasomotor responses in extracranial tissues: 1) electrical stimulation of the VII*th*, IX*th*, or Xth cranial nerve root (Gonzalez et al. 1975; Izumi and Karita 1991), 2) electrical or chemical stimulation of the preganglionic cell bodies, such as those in the superior or inferior salivatory nucleus (Nakai et al. 1993), and of

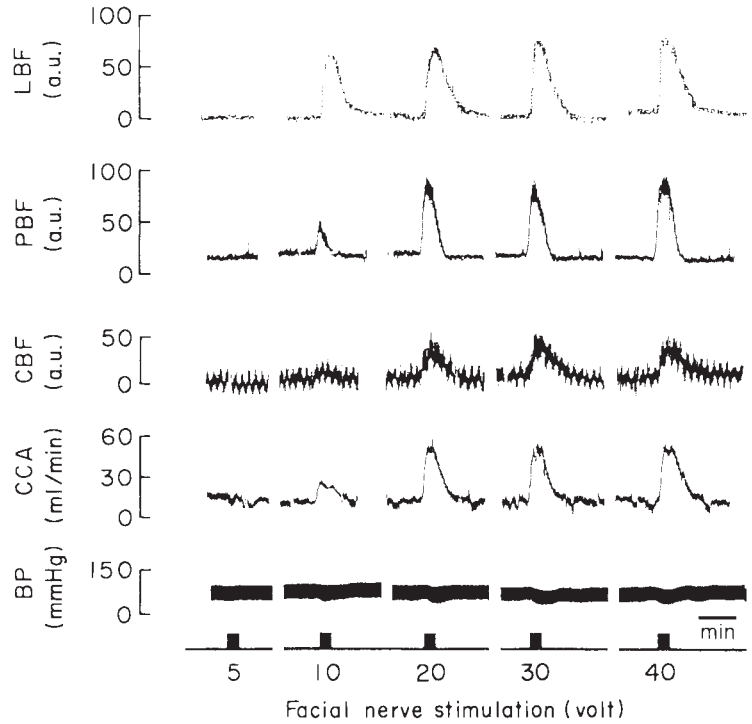

Fig. 4. Effects of electrical stimulation of the peripheral cut end of the facial (VIIth cranial) nerve root at various intensities on blood flow in the ipsilateral lower lip (LBF), palate (PBF), cerebral cortex (CBF) and common carotid artery (CCA), as well as on systemic arterial blood pressure(BP), in vago-sympathectomized cats. Parameters for lingual nerve stimulation (indicated by bars) were 2 msec, 20 Hz for 20 seconds at various intensities from 5 to 40 V. Abscissa, time (minute). Ordinate, LBF and PBF in arbitrary units (a. u.), CCA blood flow in ml/min and systemic arterial blood pressure (BP, mmHg).

Table 1. *Maximal changes in ipsilateral blood flow in lip (LBF), palate (PBF), frontal cerebral cortex (CBF) and common carotid artery (CCA) as well as in systemic blood pressure in response to electrical stimulation of lingual nerve or facial (VIIth cranial) nerve*

	Lingual nerve stimulation ($n=8$)	Facial nerve stimulation ($n=9$)
Change in LBF	16.8±1.0	14.0±1.8
Change in PBF	16.7±2.31	20.4±3.0
Change in CCA blood flow (ml/min)	58.0±5.9	54.0±5.8
Change in blood pressure (mmHg)	−8.2±5.9	−6.5±3.3
Change in CBF	1.1±0.1	2.2±0.7

The changes in blood flow in lower lip (LBF), palate (PBF) and frontal cerebral cortex (CBF) were calculated as the ratio of the peak blood flow elicited by lingual or facial nerve stimulation to the highest level of the fluctuations in baseline blood flow before nerve stimulation. The changes in common carotid artery (CCA) blood flow and in systemic blood pressure are expressed as the absolute change in the unit shown. The number of cats used is indicated in parenthesis.

the dorsal facial area (Kuo et al. 1987), locus coeruleus (Goadsby et al. 1982, 1983), dorsal raphe nucleus (Kuo et al. 1987) in the brain stem, and midbrain periaqueductal grey (Carrive and Bandler 1991), and 3) electrical stimulation of the trigeminal ganglion (in this case, parasympathetic activation occurs reflexly) (Goadsby et al. 1986; Goadsby and Duckworth 1987). However, these methods have serious drawbacks. These include surgical trauma, simultaneous stimulation of the sympathetic fibers that run in the cranial nerves, spread of electrical stimulation, and stimulation of afferent trigeminal fibers (which may cause antidromic vasodilation). The present lingual nerve-stimulation method avoids these problems by evoking reflex parasympathetic activation via excitation of afferents in a peripheral nerve. This technique is appropriate for the study of the functional role of the facial (VII*th* cranial) and glossopharyngeal (IX*th* cranial) nerves because it allows us to mimic physiological parasympathetic vasodilation and because there is less possibility of evoking antidromic vasodilation (Izumi and Karita 1992a, 1994, 1995b; Izumi 1995). Moreover, surgical trauma is less than with some other methods.

It has generally been considered that autonomic vasomotor nerves (sympathetic vasoconstrictor fibers and parasympathetic vasodilator fibers), innervate not only extracranial vascular beds such as skin and glands (salivary, lacrimal, and mucous-secreting glands), but also the intracranial vascular beds (Edvinsson 1985). Despite much investigation, however, the functional role of the facial (VII*th*) cranial nerve in controlling brain blood vessels remains uncertain (see reviews by Purves [1978] and Heistad and Marcus [1978]). Indeed, stimulation of the VII*th* cranial nerve (as well as of the superficial petrosal nerve) did not dilate pial vessels or increase CBF (Busija and Heistad 1981; Seylaz et al. 1988), and VII*th* nerve section did not have any effect on cerebrovascular reactivity to either hypercapnia or hypoxia (Hoff et al. 1977). Furthermore, some workers have looked at the responses to electrical stimulation of the facial nerve by measuring internal carotid or vertebral artery blood flow, and deduced from that the supposed changes in brain blood flow. However, such changes may reflect responses in extracranial structures, since flow in the internal carotid artery may have a significant component representing flow to extracranial tissues, and since such tissues are sensitive to neural or reflex stimuli (Heistad and Marcus 1978).

In the present experiments (Fig. 2 and Table 1), frontal CBF was not increased by ipsilateral lingual nerve stimulation, even though blood flow in the palate, which is supplied by facial vasodilator fibers, was increased by about 16-fold by the same stimulation. Our results correspond well to the results obtained by Goadsby et al. (1986) who showed that electrical stimulation of the trigeminal ganglion led to a decrease in external carotid resistance, but not to changes in internal carotid resistance in the monkey. However, we would not interpret our results according to their idea that the difference could be attributed to an antidromic activation of the trigeminal system serving the external, but not

the internal carotid circulation. This is because we have shown that our lingual nerve stimulation does not elicit antidromic vasodilation in the lower lip and palate (Goadsby and MacDonald 1985; Izumi and Karita 1994, 1995b).

The precise reasons for this inability of CBF to increase are unclear, although several possibilities may be suggested. 1) The preganglionic cell bodies whose fibers innervate the superficial brain vessels may not be influenced by somato-parasympathetic activation. This would be in harmony with the findings of Heistad and Co-workers who suggested that carotid chemoreceptor and baroreceptor reflexes do not have important effects on CBF (Heistad et al. 1976; Heistad and Marcus 1978). 2) The magnitude of the vasodilator effect may be too small to be translated into a detectable change in blood flow. 3) Surgical trauma may somehow lessen the effect of somato-parasympathetic activation. Although we cannot come to a firm conclusion on this point, we feel that the system of extrinsic nerves may not play a particularly significant role in the regulation of cerebral blood vessels. However, we cannot entierly rule out the possibility that a neurogenic vasodilator influence is exerted via the facial pathway, since a facial nerve-induced increase in CBF was observed in 4 out of 9 animals (although the magnitude of the CBF increase was much smaller than those seen in the lower lip and palate [Fig. 4]).

In conclusion, cerebrocortical blood flow was found not to be increased by electrical stimulation of the central cut end of the lingual nerve (Fig. 2 and Table 1), suggesting that there is no somato-parasympathetic reflex vasodilator mechanism in the frontal cerebral cortex. This would be in contrast to the situation in extracranial vessels, such as those in the lower lip, palate and submandibular gland (Izumi and Karita 1992b, 1993, 1994, 1995a; Izumi 1995). Moreover, changes in CCA blood flow did not correspond to those in CBF. These results indicate that changes in CCA blood flow should not be taken to be indicative of blood flow changes in the cerebral cortex.

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