Inhibitory effects of excess sympathetic activity on parasympathetic vasodilation in the rat masseter muscle

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Inhibitory effects of excess sympathetic activity on parasympathetic vasodilation in the rat masseter muscle. Am J Physiol Regul Integr Comp Physiol 293: R729–R736, 2007. First published May 30, 2007; doi:10.1152/ajpregu.00866.2006.—The present study was designed to examine the effect of sympathetic tonic activity on parasympathetic vasodilation evoked by the trigeminal-mediated reflex in the masseter muscle in urethane-anesthetized rats. Sectioning of the superior cervical sympathetic trunk (CST) ipsilaterally increased the basal level of blood flow in the masseter muscle (MBF). Electrical stimulation of the peripheral cut end of the CST for 2 min using 2-ms pulses ipsilaterally decreased in a dependent manner the intensity (0.5–10 V) and frequency (0.1–5 Hz) of the MBF. The CST stimulation for 2 min at <0.5 Hz with 5 V using 2-ms pulses seems to be comparable with the spontaneous activity in the CST fibers innervating the masseter vasculature, because this stimulation restored the basal level of the MBF to the presectioned values. Parasympathetic vasodilation evoked by electrical stimulation of the central cut end of the lingual nerve in the masseter muscle was markedly reduced by CST stimulation for 2 min with 5 V using 2-ms pulses in a frequency-dependent manner (0.5–5 Hz). Intravenous administration of phenotamine significantly reduced the vasoconstriction induced by CST stimulation in a dose-dependent manner (0.1–1 mg/kg), but pretreatment with either phenotamine or propranolol failed to affect the sympathetic inhibition of the parasympathetic vasodilation. Our results suggest that 1) excess sympathetic activity inhibits parasympathetic vasodilation in the masseter muscle, and 2) α- and β-adrenoceptors do not contribute to sympathetic inhibition of parasympathetic vasodilation, and thus some other types of receptors must be involved in this response.

superior cervical sympathetic trunk; vasoconstrictor fiber; adrenoceptors; trigeminal-mediated reflex; jaw muscle

Vasoconstriction and vasodilation are generally considered to be involved in the basic physiological adjustments to the metabolic demands of skeletal muscles, and disturbances in intramuscular blood flow may be related to muscle pain and dysfunction (7, 31). This hypothesis has been supported in recent studies that correlated muscle disorders with reductions in intramuscular blood flow (12) and muscle tissue oxygen pressure (24). These studies suggest that muscle microcirculation is disturbed in muscle disorders. Moreover, sympathetic blockade produced by local anesthesia of the stellate ganglion with bupivacaine has been reported to reduce resting pain and the number of tender points in patients with muscle dysfunction, suggesting that sympathetic activity is also an important factor in the pathogenesis of muscle disorders (2). It is therefore considered that muscle disorders may be due to a disturbance of muscle microcirculation caused by altered sympathetic activity.

Chronic pain and fatigue in the masseter muscle are well known to be the most common symptoms in craniomandibular disorders (headache, bruxism, temporomandibular disorders) (4). Sympathetic nerves derived from the superior cervical sympathetic trunk (CST) supplying blood vessels in the orofacial area have been reported to induce vasoconstrictor responses in the masseter muscles of a number of animal species (1, 10, 14, 25). These responses are completely suppressed by α-adrenoceptor blockage (10, 14). In addition, sympathetic nerves from the CST have been reported to interact with parasympathetic nerves in the regulation of blood flow to orofacial tissues (lower lip, palate, nasal mucosa, and submandibular gland) in the cat (15, 16, 23) and dog (26, 30), suggesting that the interaction between sympathetic and parasympathetic nerves may be important in the maintenance of blood flow in the orofacial area.

We recently reported the presence of parasympathetic vasodilator fibers originating from cell bodies in the otic ganglion in the rat masseter muscle. These novel parasympathetic vasodilator fibers may play an important role in the regulation of the hemodynamics of jaw muscles because the parasympathetic vasodilation evoked by activation of these fibers occurred via the trigeminal-mediated reflex (14). Chronic alterations of the hemodynamics in the masseter muscle have recently been reported to be linked to an increase in sympathetic activity for individuals with a history of chronic jaw muscle pain (5) and mental stress (13). However, it still remains unclear whether there is an interaction between sympathetic and parasympathetic nerves in the regulation of the blood flow to the masseter muscle.

The present study was designed to examine the effect of sympathetic activity on the parasympathetic vasodilation evoked by the trigeminal-mediated reflex in the masseter muscle in deeply urethane-anesthetized, artificially ventilated rats.

MATERIALS AND METHODS

Preparation of animals. Experiments were performed on adult male Wistar rats between 15 and 30 wk of age and weighing 300–450 g. After induction with inhalation anesthesia (ether), urethane (1 g/kg) in a volume of 1 ml/100 g body wt was subcutaneously injected into the backs of the animals. One femoral vein was cannulated to allow drug injection, and one femoral artery was cannulated and connected to a Statham pressure transducer to monitor the systemic arterial blood pressure (SABP) and heart rate. The anesthetized animals were

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intubated, paralyzed by intravenous injection of pancuronium bromide (Mioblock; Organon, Teknika, Arnhem, The Netherlands; 0.6 mg/kg initially, supplemented with 0.4 mg/kg every hour or so after testing the level of anesthesia; see below), and artificially ventilated via a tracheal cannula with a mixture of 50% air-50% O₂. The ventilator (model SN-480-7; Shinano, Tokyo, Japan) was set to deliver a tidal volume of 8.5–10 cm³/kg at a rate of 20–23 breaths/min, and the end-tidal concentration of CO₂ was determined by means of an infrared analyzer (Capnomac Ultima; Datex, Helsinki, Finland), as reported elsewhere (17). Rectal temperature was maintained at 37–38°C with the use of a heating pad. Before the injection of further pancuronium bromide, the depth of anesthesia was checked to be adequate by the absence of flexion response to a noxious stimulus, such as pinching the digit for ~2 s. When the depth of anesthesia was considered inadequate, additional urethane (i.e., intermittent doses of 100 mg/kg iv) was administered.

At the end of the experiment, all rats were killed by an overdose (~100 mg) of pentobarbital sodium. The experimental protocols were conducted in accordance with the Guidelines for the Care and Use of Laboratory Animals in the Health Sciences University of Hokkaido. All the animals were cared for in accordance with the recommendations in the current National Research Council guide.

Electrical stimulation of the lingual nerve and superior CST. The central cut end of the lingual nerve (LN) (Fig. 1, A) and the peripheral cut end of the superior CST (Fig. 1, B) were electrically stimulated using a bipolar silver electrode attached to an electrical stimulator (model SEN-7103; Nihon Kohden, Tokyo, Japan). For this purpose, the nerves were sectioned and stimulated unilaterally under a binocular microscope. Electrical stimulation of the CST was delivered for periods of 2 min with various voltages (0.5–10 V) at various frequencies (0.1–5 Hz) using 2-ms pulse durations. The LN was stimulated for 20 s with supramaximal voltage (20 V) at 20 Hz using 2-ms pulse durations (14) either alone, or in combination with CST stimulation. In all of the experiments, the cervical vagi and CST were cut bilaterally in the neck before the stimulation, unless otherwise noted. This ensured that only nonvagal parasympathetic effects were involved in the results reported in the present study.

Measurement of the blood flow and SABP. Changes in the blood flow of the masseter muscle (MBF; Fig. 1, c) and lower lip (LBF; Fig. 1, d) were monitored on both sides using a laser-Doppler flowmeter (LDF; FLO-C1, Omegawave, Tokyo, Japan), as described elsewhere (14, 16–18, 20, 27, 28). The probes were placed against the masseter muscle after making incisions in the cheek skin and lower lip without exerting pressure on the tissue. The masseter muscle was ascertained by the naked eye. The LDF values obtained in this way represent the blood flow in the superficial vessels of the masseter muscle (8, 22).

Electrical calibration for zero blood flow was performed for all recordings. Several gain levels could be selected and the maximum output of a particular gain level (defined electrically) was set as 100%. The analog output of the equipment does not give absolute values but shows relative changes in blood flow [for technical details and an evaluation of the LDF method see Stern et al. (33)]. The output from the various devices was continuously displayed on an eight-channel chart recorder (model W5000; Graphtec, Tokyo, Japan) at a speed of 10 mm/min. The blood flow changes were assessed by measuring the height of the response. The SABP was recorded from the femoral catheter via a Statham pressure transducer. A tachograph (model AT-610G; Nihon Kohden, Tokyo, Japan) triggered by the arterial pulse was used to monitor the heart rate.

Pharmacological agents. To determine whether the sympathetically-mediated anti-vasodilator effect was mediated via activation of α- and β-adrenoceptors, the central cut end of the LN was electrically stimulated alone, and in combination with electrical stimulation of the peripheral cut end of the CST, before and after administration of phentolamine (0.1–1 mg/kg iv), or propranolol (0.1 mg/kg iv). The magnitude of the response obtained after administration of each agent was expressed as a percentage of the control response recorded before its administration (means ± SE).

Statistical analysis. All numerical data are given as means ± SE. The statistical significance of changes in the test responses was assessed using ANOVA followed by a post hoc test [Fisher’s protected least significant difference (PLSD) test] and a contrast test. Differences were considered significant at P < 0.05. Data were analyzed using a Macintosh computer with StatView 5.0 and SuperANOVA.

RESULTS

Effects of sectioning of the CST and electrical stimulation of its peripheral cut end on the MBF, LBF, and SABP. Figure 2 shows the effects of sectioning of the left CST and electrical stimulation of its peripheral cut end on the MBF, LBF, and SABP. Under the experimental conditions in the present study, similar basal levels for MBF and LBF were recorded before the CST was sectioned (data not shown). Sectioning of the CST resulted in

![Fig. 1. Schematic representation of the sites of electrical stimulation and blood flow measurement in rats. Stimulation sites: (a) central cut end of the lingual nerve (LN); (b) peripheral cut end of the superior cervical sympathetic trunk (CST). Blood flow measurement sites: (c) masseter muscle; (d) lower lip by laser-Doppler flowmeter (LDF). The continuous lines indicate (A) trigeminal sensory inputs to the brain stem; (B) parasympathetic vasodilator fibers to the masseter muscle and lower lip from the salivatory nuclei (SN). The dashed lines indicate (C) sympathetic vasoconstrictor fibers to both masseter muscle and lower lip from the CST. OG, otic ganglion; SCG, superior cervical ganglion; TG, trigeminal ganglion; Vsp, trigeminal spinal nucleus; V, trigeminal nerve root; IX, glossopharyngeal nerve root.](http://ajpregu.physiology.org/Downloaded from http://ajpregu.physiology.org/)
a continuous (Fig. 2, a1) and a significant increase in the basal level of MBF on the left side, but not of LBF (for MBF, n = 5, P < 0.001; for LBF, n = 5, NS; CSTs in Fig. 3B). Electrical stimulation of the sectioned CST for 2 min with 5 V at 0.5 Hz using 2-ms pulses induced a decrease in both MBF and LBF on the left side (Fig. 2, a2). Figure 3 shows the mean data ± SE for the effects of CST stimulation on both MBF and LBF on the left side when the CST stimulation was delivered for 2 min at various intensities (0.5–10 V; Fig. 3A) and at various frequencies (0.1–5 Hz; Fig. 3B) using 2-ms pulses. Intensity-response relationships were generated using stimulus trains at 5 Hz. Frequency-response relationships were generated using stimulus trains at 5 V. The maximal change in MBF in response to CST stimulation was taken as 100%. A significant decrease in both MBF and LBF took place above 2 V (for MBF, F(5,18) = 11.92, n = 4 in each group, P < 0.0001; for LBF, F(5,18) = 6.76, n = 4 in each group, P < 0.001; Fig. 3A). CST stimulation at 5 V showed a significant effect on the decrease in both MBF and LBF above 0.2 and 1 Hz, respectively, [for MBF, F(6,28) = 114.5, n = 5 in each group, P < 0.0001; for LBF, F(6,28) = 10.07, n = 5 in each group, P < 0.0001; Fig. 3B]. On the right side, CST stimulation had no effect on either MBF or LBF (Fig. 2). The resting mean SABP (means ± SE) before each treatment was 99.4 ± 6.4 mmHg. After sectioning of the CST, resting mean SABP was 102.1 ± 6.8 and after electrical stimulation of the sectioned CST for 2 min with 5 V at 5 Hz using 2-ms pulses, it was 90.6 ± 4.9 mmHg. There was no significant difference in the resting mean SABP before and after each treatment [F(2,9) = 0.95, n = 4 in each group, NS].

Effects of CST stimulation on increases in MBF and LBF evoked by electrical stimulation of the central cut end of the LN. Electrical stimulation of the central cut end of the left LN (Fig. 1, a) evoked an increase in both MBF and LBF on the left side for 20 s with supramaximal intensity (20 V) at 20 Hz using 2-ms pulses, as described in our previous report (14). Figure 4 shows the effect of electrical stimulation of the left sectioned CST for 2 min with 5 V at various frequencies (0.1–5 Hz) using 2-ms pulses on the increase in both MBF (A) and LBF (B) evoked by LN stimulation. The mean data ± SE of changes in MBF and LBF evoked by LN stimulation in combination with CST stimulation at 0.1, 0.2, 0.5, 1, 2, and 5 Hz, expressed as percentages of the control response without CST stimulation, were 105.8 ± 13.9 and 117.6 ± 17.5, 73.3 ± 17.4 and 94.1 ± 6.1, 38.3 ± 12.0 and 90.3 ± 8.8, 22.0 ± 7.6 and 95.3 ± 4.2, 12.3 ± 2.8 and 92.4 ± 4.1, and 10.2 ± 4.7 and 87.0 ± 5.7%, respectively. CST stimulation above 0.2 Hz showed a significant inhibitory effect on the increase in MBF evoked by LN stimulation, but this was not observed in LBF [for MBF, F(6,28) = 16.52, n = 5 in each group, P < 0.0001; for LBF, F(6,28) = 0.1, n = 5 in each group, NS; Fig. 5A]. These responses in MBF returned almost to the control level 10 min after the cessation of CST stimulation at 5 Hz (Figs. 4 and 5A). We observed a “rebound” increase in MBF after electrical stimulation of the CST was terminated (Fig. 4A). The termination of CST stimulation at levels above 0.5 Hz resulted in a significant effect on the increase in MBF, but this was not observed in the LBF [for MBF, F(5,24) = 33.69, n = 5 in each group, P < 0.0001; for LBF, F(5,24) = 0.8, n = 5 in each group, NS; Fig. 5B]. The mean changes in SABP following LN stimulation were too slight to account for the blood flow changes measured by the present methods (13.1 ± 0.6 mmHg, n = 5; data not shown).

Effects of pharmacological blocking agents. Electrical stimulation of the central cut end of the left LN was delivered for 20 s with supramaximal intensity (20 V) at 20 Hz using 2-ms pulses. The peripheral cut end of the left CST was stimulated for 2 min with 5 V at >0.5 Hz using 2-ms pulses. The stimulus frequency (>0.5 Hz) of the CST was chosen to initiate the inhibitory effect on the increase in MBF evoked by LN stimulation. Figure 6 shows the effects of intravenous administration of phentolamine (0.1 and 1 mg/kg; Fig. 6A) and propranolol (0.1 mg/kg; Fig. 6B) on changes in MBF on the left side evoked by LN stimulation alone (a1 and b1), and in
combination with CST stimulation (a2 and b2). The mean data ± SE of the changes in MBF before and 10 min after administration of each agent were expressed as a percentage of the control response recorded before administration (Fig. 6C). The increases in MBF evoked by LN stimulation alone were not affected by phentolamine and propranolol at 0.1 mg/kg but were significantly reduced by pretreatment with phentolamine at 1 mg/kg \(F(3,12) = 5.8, n = 4\) in each group, \(P < 0.01\); Fig. 6C]. The decrease in MBF elicited by CST stimulation was significantly reduced by phentolamine in a dose-dependent manner (0.1 and 1 mg/kg) \(F(3,16) = 13.9, n = 5\) in each group, \(P < 0.0001\); Fig. 6C]. The magnitude of the rise in MBF evoked by LN stimulation in combination with CST stimulation was unchanged by pretreatment with either phentolamine (0.1 and 1 mg/kg), or propranolol \(F(3,16) = 0.3, n = 5\) in each group, NS; Fig. 6C]. The increase in MBF evoked by LN stimulation alone was significantly larger than that in combination with CST stimulation, regardless of the presence or absence of each drug \((P < 0.001, \text{ANOVA followed by a contrast test}; \text{Fig. 6C]). These responses in MBF returned almost to the control level 30–60 min after the administration of each drug (data not shown). The resting mean SABP (means ± SE) before pretreatment was 100.6 ± 6.3 mmHg and 10 min after administration of phentolamine (0.1 and 1 mg/kg); 97.2 ± 5.7 and 64.7 ± 2.7, or propranolol; 109.4 ± 9.9 mmHg, respectively. There was a significant difference in the resting mean SABP before and after the administration of phentolamine at 1 mg/kg \([F(3,20) = 8.4, n = 6\) in each group, \(P < 0.001\]).

**DISCUSSION**

The blood flow changes induced by electrical stimulation of both the peripheral cut end of the CST and the central cut end of the LN in the present study appeared not to be secondary to changes in the SABP because no significant changes in the SABP were observed during stimulation (see RESULTS). In this paper, we therefore refer to the CST-stimulated changes as “vasoconstriction” and to the LN-stimulated changes as “vasodilation.”

Sympathetic outflow to the blood vessels in the skeletal muscles is known to be under tonic control of the arterial and cardiopulmonary baroreflexes (6). In the present study, CST stimulation for 2 min appears to mimic the physiological forms of spontaneous tonic activity in the CST fibers supplying the vasculature in the orofacial area, because vasoconstriction in the masseter muscle and lower lip induced by CST stimulation reached stable levels within <1 min and sustained these levels during the stimulation (Figs. 2, 4 and 6, A and B).

Under our experimental conditions, stimulation of the CST for 2 min at <0.5 Hz with 5 V using 2-ms pulses seems to be comparable with the spontaneous activity in the CST fibers innervating the masseter vasculature, because this stimulation restored the basal level in the MBF to the presectioned values (Figs. 2 and 3B). This observation is consistent with a report that found that the frequency of extracellularly recorded spontaneously active postganglionic units in the rat hindlimb is ~1 Hz (11). Conversely, the LBF was consistently unchanged by sectioning of the CST in all of the animals examined in the present study (Figs. 2 and 3B), suggesting that the CST fibers supplying the vasculature in the lower lip have either none or a very low level of spontaneous activity under physiological conditions. This is consistent with previous observations that the blood flow in the lower lip, palate, submandibular gland, and tongue is largely unaffected by sectioning of the CST in the cat (16).

The parasympathetic vasodilation evoked by LN stimulation in the masseter muscle decreased markedly during CST stimulation for 2 min with 5 V using 2-ms pulses as the frequency increased from 0.5 to 5 Hz and had almost disappeared at a frequency of 5 Hz (Figs. 4A and 5A). This indicates that excess sympathetic activity inhibits the parasympathetic vasodilation evoked by the trigeminal-mediated reflex in the masseter muscle. This inhibitory effect on parasympathetic vasodilation was not observed in the lower lip (Figs. 4B and 5A). The precise mechanism by which excess sympathetic activity inhibits parasympathetic vasodilation in the masseter muscle, but not in the lower lip, still remains unclear. However, the masseter muscle
seems to differ from the lower lip in sympathetic-parasympathetic interaction, because 1) there is spontaneous tonic activity in the CST fibers supplying the vasculature in the masseter muscle, but not in the lower lip (Figs. 2 and 3B), 2) parasympathetic vasodilation in the masseter muscle is partly sensitive to the antimuscarinic agent atropine (0.1 mg/kg) but not in the lower lip (14, 16–18, 20, 27, 28), and 3) it has been suggested that muscle vasoconstrictor neurons consist of larger sympathetic motor units and innervate a larger volume of vasculature compared with cutaneous vasoconstrictor neurons (9). Considering these different physiological and anatomical observations of sympathetic innervation between the masseter muscle and other orofacial tissue such as the lower lip, it is understandable that the hemodynamics of the masseter muscle could be susceptible to sympathetic activity.

Pretreatment with phentolamine significantly reduced the vasoconstriction induced by CST stimulation in a dose-dependent manner (0.1–1 mg/kg), but pretreatment with either phentolamine or propranolol (0.1 mg/kg) failed to affect the inhibitory effect on parasympathetic vasodilation in the masseter muscle (Fig. 6). The changes in the end-tidal concentration of CO₂ following each drug treatment (from 45 to 40 mmHg) did not account for the blood flow changes measured by the present method (data not shown). These results suggest that α- and β-adrenoceptors do not contribute to the sympathetic inhibition of parasympathetic vasodilation, and thus some other types of
receptors must be involved in this response. Although some researchers suggest that, in addition to catecholamine, neuropeptide Y, galanin, and ATP may act as nonadrenergic sympathetic cotransmitters (3, 23, 32), it is still unclear whether these transmitters are involved in this inhibitory response. Further investigations will be necessary to establish the neural mechanisms underlying the sympathetic inhibition of parasympathetic vasodilation.

LN stimulation-induced parasympathetic vasodilation in the masseter muscle was significantly reduced by intravenous administration of phentolamine (1 mg/kg) accompanied by a marked reduction in the resting mean SABP (from 100.6 ± 6.3 to 64.7 ± 2.7 mmHg). The fall in the magnitude of parasympathetic vasodilation caused by phentolamine would not be mediated via α-adrenoceptors because parasympathetic vasodilation during CST stimulation remained the same regardless of the presence or absence of phentolamine (Fig. 6, A and C). It is therefore likely that this response is secondary to a reduction in the resting SABP caused by the administration of phentolamine. This is supported by previous observations that the magnitude of parasympathetic vasodilation in the lower lip of rabbits was reduced by pretreat-
ment with phentolamine at 1 mg/kg accompanied by a significant decrease in the resting SABP (34). These observations suggest that the magnitude of parasympathetic vasodilation in orofacial tissue may depend on the resting SABP.

A rebound increase in MBF was observed after the completion of CST stimulation for 2 min with 5 V using 2-ms pulses at high frequencies (>0.5 Hz), but not at low frequencies (0.1–0.2 Hz) (Figs. 4A and 5B). This increase disappeared when the vasocostriction induced by CST stimulation was suppressed with the administration of phentolamine (1 mg/kg) (Fig. 6A), suggesting that the rebound MBF increase may be reactive hyperemia in response to changes in local oxygen pressure and metabolite concentration during a period of reduced MBF.

The physiological significance of parasympathetic vasodilation in the hemodynamics of the MBF is unclear, because it is difficult to activate parasympathetic pathways to the masseter vasculature through natural stimuli (such as pinching the tongue or placing a drop of acid) under our experimental conditions (deeply urethane-anesthetized and artificially ventilated). However, evocation of parasympathetic vasodilation by pinching, heat, or chemical stimulation (capsaicin, nicotine, or ammonia) has previously been reported in some orofacial areas, such as the lower lip (21) and the nasal mucosa (19). The results were similar to the parasympathetic vasodilation evoked by electrical stimulation of the LN in anesthetized, artificially ventilated cats. It is therefore likely that evoking parasympathetic vasodilation in the MBF would involve nociceptive, thermal, and tactile sensations occurring during complex movements such as mastication, speech, and swallowing. Although the underlying mechanisms of MBF disorders are not fully understood, ischemia may play a role in their development because blood flow impairment occurs, even with low levels of activity in the MBF (29). Under such conditions, a blood flow increase to the masseter muscle, which occurs via parasympathetic reflex vasodilation, could be related to the maintenance of MBF. Thus, the inhibitory effect of excess sympathetic activity on parasympathetic vasodilation may affect the hemodynamics of the MBF, suggesting an important role in the etiology of MBF disorders.

In conclusion, the present study found that excess sympathetic activity inhibits the parasympathetic vasodilation evoked by the trigeminal-mediated reflex in the masseter muscle but not in the lower lip, suggesting that the hemodynamics of the masseter muscle are susceptible to sympathetic activity. It is likely that α- and β-adrenoceptors do not contribute to sympathetic inhibition of parasympathetic vasodilation, and thus some other types of receptors must be involved in this response. Further studies of the neural mechanisms underlying the sympathetically mediated antivasodilator effect would provide data that would enable a better understanding of the etiology of jaw muscle disorders.

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