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European Journal of Pharmacology 440 (2002) 53–59

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Differential neural activation of vascular α-adrenoceptors in oral tissues of cats

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Received 29 October 2001; received in revised form 30 January 2002; accepted 8 February 2002

Abstract

The aim of this study was to determine the relative contribution of α_1- and α_2-adrenoceptors involved in sympathetic-evoked vasoconstrictor responses in tissues perfused by the lingual arterial circulation in pentobarbital anesthetized cats. Blood flow in the lingual artery was measured by ultrasonic flowmetry. Laser–Doppler flowmetry was utilized to measure oral tissue vasoconstrictor responses in the maxillary gingiva and from the surface of the tongue. Electrical stimulation of the preganglionic superior cervical sympathetic nerve resulted in frequency-dependent blood flow decreases at all three sites. These responses were stable over time and were uniformly antagonized by administration of phentolamine (0.3–3.0 mg kg^{-1}). The selective α_1-adrenoceptor antagonist, prazosin (10–300 μg kg^{-1}), attenuated vasoconstriction in the lingual artery and gingiva, but was ineffective in blocking vasoconstriction in the tongue. Subsequent administration of rauwolscine (300 μg kg^{-1}) antagonized remaining vasoconstrictor responses. In contrast, rauwolscine (10–300 μg kg^{-1}), given alone, blocked evoked vasoconstriction in the tongue, and was without effect on gingival or lingual artery vasoconstrictor responses. Subsequent administration of prazosin (300 μg kg^{-1}) largely antagonized remaining neurally elicited responses. These results suggest that neural vasoconstrictor responses in some regional vascular beds in the cat oral cavity are mediated by both α_1- and α_2-adrenoceptors. In contrast, tongue surface vasoconstrictor responses to sympathetic nerve activation appear to be mediated primarily by α_2-adrenoceptors.

Keywords: Laser–Doppler flowmetry; Ultrasonic flowmetry; α-Adrenoceptor subtype; Sympathetic nerve stimulation; Tongue circulation; Gingival circulation; Lingual artery; Phentolamine; Prazosin; Rauwolscine

1. Introduction

Electrical stimulation of the cervical sympathetic nerve trunk uniformly produces vasoconstriction in tissues of the oral cavity in all species studied (Hellekant, 1976; Pleschka, 1984; Izumi et al., 1990; Kerezoudis et al., 1995; Izumi and Ito, 1998). It is clear that α-adrenoceptors are involved in vascular constriction in the gingiva of cats and rats (Edwall and Kindlova, 1971; Eccles and Wallis, 1976; Izumi and Karita, 1990; Izumi et al., 1990; Kerezoudis et al., 1995). However, we have little understanding of the specific subtypes of adrenoceptors involved. In addition, little is known regarding neurochemical mechanisms underlying neural vasoconstriction in other tissues of the oral cavity. This is largely because required frequency– and dose–response relationships could not readily be ascertained with techniques previously available.

In the present experiments, we utilized more recently developed methodology in order to continuously measure blood flow directly from a lingual artery (ultrasonic flowmetry) and from the surface of the gingiva and tongue (laser–Doppler flowmetry). Attention was focused on physiological and pharmacological analysis of the role of the sympathetic nervous system in regulation of blood flow in these tissues of the oral cavity. Our results suggest a role for both α_1- and α_2-adrenoceptors in neurogenic control of vascular tone in the gingiva and other tissues perfused by the lingual artery. In contrast, sympathetic neurogenic control of the vasculature of the tongue surface appears to involve mainly α_2-adrenoceptor mechanisms.

2. Materials and methods

2.1. General

Adult cats of either sex were anesthetized with pentobarbital (36 mg kg^{-1}, i.p.). All animals were treated in a

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0014-2999/02/$ - see front matter
PII: S0014-2999(02)01364-X

manner consistent with the regulations of the US Public Health Service, with experimental protocols approved by the University of Oklahoma Institutional Animal Use and Care Committee. A femoral artery and vein were cannulated for measurement of systemic arterial blood pressure (Statham P23 transducer; Hato Rey, P.R.) and for intravenous drug administration, respectively. Heart rate was derived from the femoral arterial pulse wave by means of a cardiotachograph (Grass 7P4; Quincy, MA). All physiological responses were recorded on a polygraph (Grass model 7). Following cannulation of the trachea, the animals were mounted in a stereotaxic apparatus (David Kopf; Tujunga, CA), ventilated with a respirator (Harvard Apparatus; Holliston, MA), and immobilized with gallamine triethiodide (4 mg kg^{-1}, i.v.). Body temperature was maintained at 37 °C using a heating pad connected to a thermistor measuring rectal temperature and controlled with a feedback circuit (Yellow Springs Instrument; Yellow Springs, OH).

2.2. Assessment of blood flow changes in the lingual artery

Blood flow in a lingual artery was measured by ultrasonic flowmetry using a transit-time ultrasonic flowmeter (Transonic Systems, Model T106; Ithaca, NY) coupled to a flow probe (1RB1580) designed for vessels of approximately 1 mm diameter. With this technique, the blood vessel is exposed and placed within the window of the probe, which houses two ultrasonic transducers and a fixed acoustic reflector. The flowmeter analyzes the signals as ''transit-time'' it takes for the ultrasound wave to travel from one transducer to the other. For comprehensive technical details and validation of this technique, see Hartman et al. (1994).

2.3. Assessment of blood flow changes in the gingival and tongue surface

Blood flow from the tongue surface and the maxillary gingiva was simultaneously measured by laser–Doppler flowmetry (Baab et al., 1986) using Perimed (PF-2; Stockholm) and Laserflow (BPM 403A-2; St. Paul, MN) laser–Doppler flowmeters. Tip size was approximately 1 mm diameter for both probes. The laser–Doppler technique exposes a small area of the measured tissue to a coherent laser light, which penetrates to a depth of approximately 0.5 mm. As this light is reflected from moving red blood cells, it undergoes a Doppler frequency shift that is recorded as Doppler-beat frequencies at the photodetector in the probe tip, and converted into a numerical value proportional to blood flow within the illuminated volume of tissue.

In order to avoid measurement of muscle blood flow, the lingual probe was placed on the lateral edge of the tongue approximately 3 mm from the tip. This lateral placement is over two closely adjoining cutaneous vascular beds with little muscle between them (as would be found in more central sites on the tongue). The gingival probe was placed near the first canine tooth on the ipsilateral maxillary gingiva. The contralateral lingual artery was tied off in order to decrease the potential of blood flow emanating from the contralateral side (Webb et al., 1979). Tissues were coated with mineral oil to prevent desiccation and improve optic coupling between the tissue and probe. Once in place, the probes were kept in the same location throughout the experiment. To insure stability, the animals were allowed to rest 15 min before experimental manipulation. At the conclusion of the experiments, ''zero'' blood flow measurements were obtained after the animals were euthanized.

2.4. Sympathetic nerve stimulation

Electrical stimulation of the ipsilateral preganglionic cervical sympathetic nerve was used for physiological activation of adrenoceptor mechanisms. The sympathetic nerve trunk was carefully dissected free of the vagus nerve and crushed proximally. A pair of silver wire stimulating electrodes were placed under the nerve at the mid-cervical level and the stimulation site was immersed in warm mineral oil. Square wave pulses of supramaximal voltage and duration (6–10 V; 2 ms) were derived from a Grass S88 stimulator and Grass SIU5 isolation unit (Grass Instruments). Trains of stimuli (10 s) were applied with the frequency varied from 2 to 32 Hz. Antagonists were administered intravenously with at least 15 min allowed to reach steady state.

2.5. Drugs and statistical analyses

The following drugs were used: gallamine triethiodide, prazosin hydrochloride, rauwolscine hydrochloride, and phentolamine mesylate. Compounds were purchased from Sigma, St. Louis, MO, USA. All drug solutions were prepared in physiological saline with the exception of prazosin [2.5% glucose (w/v):2.5% glycerol (v/v)]. Drug dosages refer to the respective salts.

Data are reported as means ± S.E.M. Measurements of the area of the vasoconstrictor curves (AUC) indicate relative areas representing changes in blood flow in response to electrical nerve stimulation. The area of each vasoconstrictor response was compared with the initial control responses in each preparation. These values comprise not only the magnitude (amplitude) but also the time component (duration) of the responses. Measured values are reported as a percentage of the initial control responses. A Sigma digital tablet (Jandel Scientific; Corte Madera, CA) linked with appropriate software was utilized to make these measurements. Changes of blood pressure, heart rate and basal blood flows, before and after nerve section and antagonist administration were analyzed using Student's *t*-test for paired comparisons. Dose–response relationships were compared using analysis of variance. In all cases, values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Blood flow measurements in oral tissues and effects of acute sympathectomy

Lingual arterial (ultrasonic flowmetry) and tongue and gingival (laser–Doppler flowmetry) blood flows were measured before and after section of the ipsilateral preganglionic cervical sympathetic nerve in 26 anesthetized cats. Acute sympathectomy produced a sustained, statistically significant elevation of lingual arterial blood flow to 152% of control levels ($P<0.01$) from 1.3 ± 0.2 to 1.8 ± 0.2 ml min^{-1} of control levels, respectively. In contrast, preganglionic nerve section did not result in increased blood flow to the gingiva or to the tongue surface. At these two sites, 10 min after nerve section, blood flows were $104 \pm 5\%$ and $109 \pm 14\%$ of initial control levels, respectively.

3.2. Responses to preganglionic sympathetic nerve stimulation

Electrical stimulation of the preganglionic cervical sympathetic nerve produced vasoconstrictor responses that were similar in relative magnitude at all three measurement sites (Fig. 1). A composite representation of combined frequency–response curves is shown in Fig. 2. Maximal neurally elicited responses were uniformly seen at about 32 Hz (Fig. 2). For the following experiments, frequencies of electrical stimulation producing 50–80% of the maximal responses were chosen. Depending on the sensitivity of the individual preparation, these were usually between 4 and 10 Hz. As a control, responses were evoked at 2-min intervals and followed for 45 min in six cats. Bolus injections of saline were administered to mimic drug injection periods. There were no significant declines in the magnitude of these vasoconstrictor responses. For example, after 45 min, vasoconstriction was $112 \pm 17\%$, $99 \pm 9\%$, and $84 \pm 15\%$ of control for the tongue, lingual artery and gingiva, respectively.

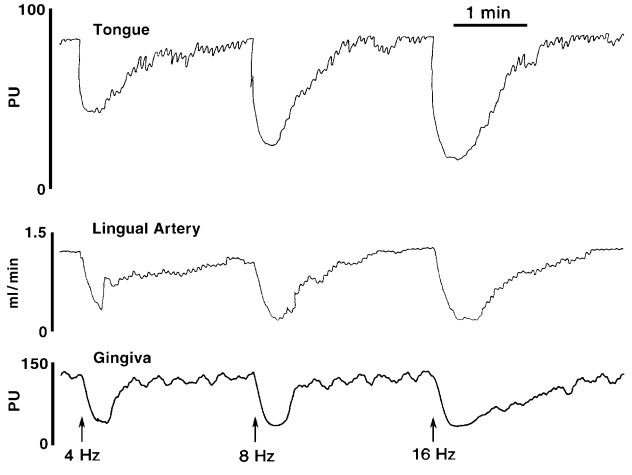

Fig. 1. Effects of increasing frequencies (4–16 Hz) of electrical stimulation of the preganglionic cervical sympathetic nerve on oral tissue blood flow measured using laser–Doppler flowmetry (tongue and maxillary gingiva) and ultrasonic flowmetry (lingual artery) in a pentobarbital anesthetized cat. Laser–Doppler recordings are expressed in arbitrary perfusion units (PU). Lingual arterial blood flow is expressed in absolute units (ml/min). Note graded frequency-related vasoconstrictor responses that are most clearly distinguished when represented as alterations of area under the curve (AUC). Neither systemic arterial blood pressure nor heart rate was altered by presentation of these trains of stimuli (10 V; 2 ms; 10 s trains).

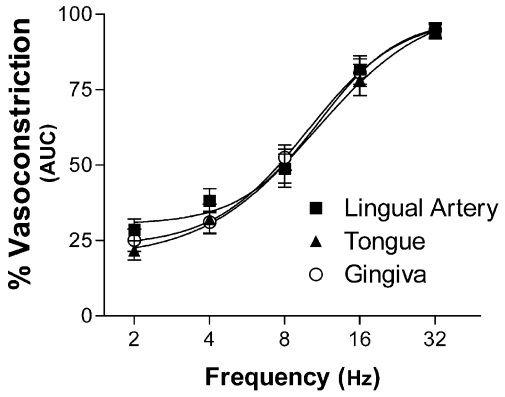

Fig. 2. Composite frequency–response relationships for oral tissue vasoconstriction responses to electrical stimulation of the preganglionic cervical sympathetic nerve trunk (2–32 Hz) in 18 pentobarbital anesthetized cats. Values represent percentage of maximal vasoconstriction in response to nerve stimulation and are expressed as area under the response curve (AUC). Solid squares represent frequency-related vasoconstrictor responses measured from the ipsilateral lingual artery using ultrasonic flowmetry. Open circles and solid triangles represent vasoconstrictor responses measured from the maxillary gingiva and tongue surface using laser–Doppler flowmetry. Note similarity in responsiveness between the different measurement sites. Stimulation parameters: 6–10 V; 2 ms pulse width; 10 s trains of pulses. Values represent mean response ± S.E.M.

3.3. Changes in oral tissue blood flow in response to α-adrenoceptor blockade

In order to determine the nature of the α-adrenoceptors mediating these vasoconstrictor responses, both nonselective and selective antagonists were employed. For nonselective adrenoceptor blockade, we chose phentolamine. As shown in Fig. 3, intravenous administration of phentolamine (0.3, 1.0 and 3.0 mg kg^{-1}) caused an equivalent dose-dependent blockade of all three neuronally elicited vasoconstrictor responses. Phentolamine produced a significant hypotension at the two higher doses (from 125 ± 7 to 108 ± 6 and 105 ± 5 mm Hg, respectively).

The contribution made by activation of selective α-adrenoceptor subtypes was evaluated by use of prazosin and rauwolscine (given both alone and in combination) on neurally evoked oral tissue vasoconstrictor responses. A typical example of these experiments is shown in Fig. 4.

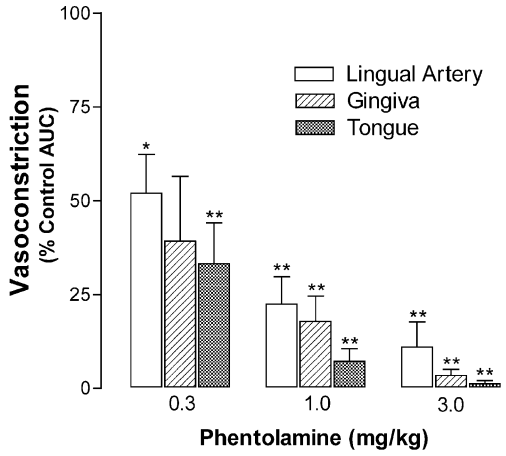

Fig. 3. Composite effects of cumulative intravenous administration of phentolamine (0.3–3.0 mg kg^{-1}) on lingual arterial, gingival, and tongue blood flow in pentobarbital anesthetized cats. Stimulation parameters set to produce responses between 50% and 80% of maximal. Values represent means of the area of the vasoconstrictor responses (AUC) in comparison to individual control values. Horizontal bars represent S.E.M. for six animals. * $P<0.05$; ** $P<0.01$.

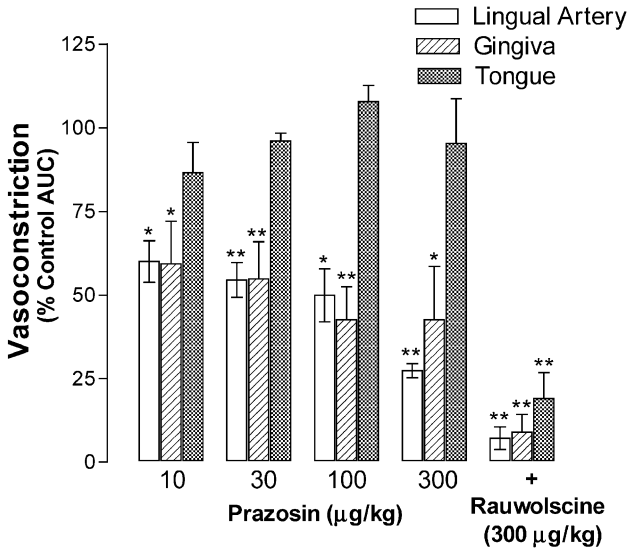

Fig. 5. Composite effects of cumulative intravenous administration of prazosin (10–300 μg kg^{-1}) on lingual arterial, gingival, and tongue blood flow in pentobarbital anesthetized cats. Stimulation parameters set to produce responses between 50% and 80% of maximal. Values represent means of the area of the vasoconstrictor responses (AUC) expressed as percentage of individual control values. Horizontal bars represent S.E.M. for five to seven animals. Note antagonism of lingual artery and gingival responses by subsequent prazosin administration (α_1-adrenoceptor blockade) and subsequent antagonism of tongue vasoconstriction produced by rauwolscine (α_2-adrenoceptor blockade). * $P<0.05$; ** $P<0.01$.

Fig. 5 shows effects of cumulative administration of the α_1-adrenoceptor antagonist, prazosin (10–300 μg kg^{-1}) followed by addition of the α_2-adrenoceptor antagonist, rauwolscine (300 μg kg^{-1}). In these experiments (Fig. 5), prazosin caused a significant reduction in evoked vasoconstrictor responses in the lingual artery and gingiva, even at the lowest dose level (10 μg kg^{-1}). Higher doses of prazosin (30–300 μg kg^{-1}) produced little additional blockade of vasoconstriction at these two sites. In contrast, vasoconstrictor responses in the tongue were not antagonized by any dose of prazosin administered. Subsequent administration of rauwolscine (300 μg kg^{-1}) almost totally abolished evoked vasoconstrictor responses at all three recording locations.

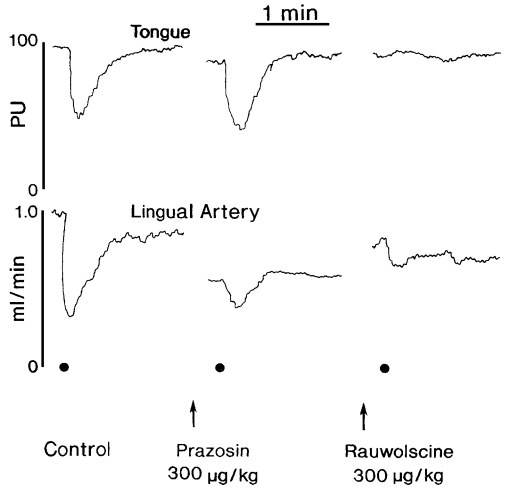

Fig. 4. Effects of electrical stimulation of the preganglionic cervical sympathetic nerve on tongue and lingual artery blood flow as measured using laser–Doppler and ultrasonic flowmetry in a pentobarbital anesthetized cat. PU indicates arbitrary perfusion units for laser–Doppler recordings. Upper panels represent vasoconstrictor responses measured from the tongue under control conditions (4 Hz; 10 V; 2 ms; 10 s trains) and after intravenous administration of prazosin (300 μg kg^{-1}) followed by rauwolscine (300 μg kg^{-1}). Lower panels represent responses and drug effects simultaneously obtained from the ipsilateral lingual artery. Note resistance of tongue vasoconstrictor responses to α_1-adrenoceptor blockade with prazosin and subsequent sensitivity to α_2-adrenoceptor blockade with rauwolscine.

Fig. 6 shows the converse experiments, effects of cumulative administration of the α_2-adrenoceptor antagonist, rauwolscine (10–300 μg kg^{-1}), followed by addition of the α_1-adrenoceptor antagonist, prazosin (300 μg kg^{-1}). In these experiments, initial administration of rauwolscine (10–300 μg kg^{-1}) selectively antagonized vasoconstrictor responses elicited from the tongue surface in a dose-dependent fashion with no significant effect on constrictor responses recorded from the lingual artery or gingiva. Subsequent administration of prazosin (300 μg kg^{-1}) almost totally abolished evoked vasoconstrictor responses from all three recording locations.

As with phentolamine, prazosin produced a significant hypotension at the three higher doses (from 132 ± 12 to 98 ± 7, 92 ± 6, and 88 ± 7 mm Hg respectively). Rauwols-

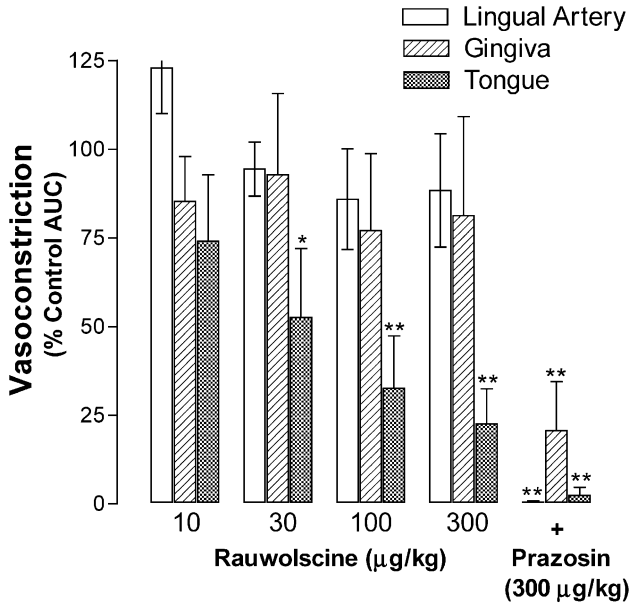

Fig. 6. Composite effects of cumulative intravenous administration of rauwolscine (10–300 μg kg^{-1}) on lingual arterial, gingival, and tongue blood flow in pentobarbital anesthetized cats. Stimulation parameters set to produce responses between 50% and 80% of maximal. Values represent means of the area of the vasoconstrictor responses (AUC) expressed as percentage of individual control values. Horizontal bars represent S.E.M. for six animals. Note selective antagonism of tongue vasoconstriction produced by rauwolscine (α_2-adrenoceptor blockade) and subsequent antagonism of lingual artery and gingival responses by subsequent prazosin administration (α_1-adrenoceptor blockade). * $P<0.05$; ** $P<0.01$.

cine did not produce significant hypotension at any dose administered.

4. Discussion

After section of the cervical sympathetic nerve trunk, ipsilateral lingual arterial blood flow was significantly enhanced. The observed 50% increase in blood flow suggests that there is appreciable tonic sympathetic nerve activity to the vascular beds perfused by this artery, even in the pentobarbital anesthetized cat. In contrast, blood flow in the tongue and gingiva was unaffected by sympathetic nerve section, indicating a very low level of sympathetic neuronal tone to these more terminal vascular beds.

The differential response to sympathetic nerve section is consistent with observations by others. For example, Izumi and Ito (1998) found blood flow in the cat common carotid artery to increase by 36% following acute sympathectomy. In the same cats, blood flows to the lower lip, submandibular gland, palate, and tongue were not changed by nerve section. Others observed a 50% increase in maxillary arterial blood flow in cats (Lacroix et al., 1994) and an even larger increase (300+%) in the nasal mucosa of rats (Kawarai and Koss, 2001) in response to sympathetic nerve section. In contrast, blood flow to the choroid of the eye of both cats and rats (Koss and Gherezghigher, 1993; Kawarai and Koss, 1998) as well as to cutaneous vascular beds in the cat (Koss et al., 1991; Karasawa and Koss, 1993) is unaffected by acute sympathectomy.

Taken together, the above results support the conclusion that there is a highly differential degree of tonic sympathetic activity that seems to depend upon the particular vascular bed under investigation. There are, however, other potentially confounding issues such as the degree of anesthesia and use of different methodologies to measure blood flow.

Electrically evoked vasoconstriction in oral tissues also have been reported by others with regard to blood flow in the cat gingiva (Edwall and Kindlova, 1971; Izumi and Karita, 1990; Izumi et al., 1990) and tongue (Erici et al., 1952; Alm and Bill, 1973; Eccles and Wallis, 1976; Izumi and Ito, 1998). Similar responses are also seen in other species with vasoconstriction observed in the vasculature of the rabbit tongue (Linder, 1981) and gingiva of the rat (Kerezoudis et al., 1995).

Postjunctional α_1- and α_2-adrenoceptors coexist in the systemic vasculature with both receptor subtypes mediating vasoconstriction (Drew and Whiting, 1979). Originally, it was proposed that α_1-adrenoceptors are preferentially innervated and that α_2-adrenoceptors are only ''extrasynaptic'', primarily activated by circulating catecholamines (Langer et al., 1981; Timmermans and Van Zwieten, 1981). More recently, however, neuronally mediated activation of both α_1- and α_2-adrenoceptors has been reported in many in vivo systems (see Koss et al., 1991).

In this study, both α_1- and α_2-adrenoceptors appeared to mediate neurogenic vasoconstriction in gingival tissues and, potentially, other vascular beds perfused by the lingual artery. The most dramatic finding was the observation showing the vasculature of the tongue surface to be almost exclusively controlled by α_2-adrenoceptor mechanisms. This is similar to what is seen in the cat cutaneous circulation (Koss, 1990; Koss et al., 1991; Karasawa and Koss, 1993). In contrast, we have previously shown that other vascular systems activated by the cervical sympathetic nerves (e.g., cat and rat choroid and rat nasal mucosal circulations) exclusively utilize α_1-adrenoceptor mechanisms. The present observations demonstrating differential involvement of innervated α_2-adrenoceptors are in agreement with these results, as well as with those of others showing that postjunctional α_1- and α_2-adrenoceptors are not evenly distributed throughout the vascular system (Horn et al., 1982).

The present study is the first concerning characterization of innervated adrenoceptor subtypes of the vasculature of the cat oral cavity. Clearly, sympathetic nerve stimulation produced vasoconstriction by activation of α-adrenoceptors as evoked vasoconstrictor responses were antagonized by administration of phentolamine in a dose-related fashion. This is consistent with previous reports with regard to phentolamine blockade of neurogenic gingival and tongue vasoconstriction in cats (Edwall and Kindlova, 1971; Eccles and Wallis, 1976; Izumi and Karita, 1990). There is one

study in rats (consistent with the present observations in cats) in which prazosin greatly reduces sympathetic-elicited gingival vasoconstriction (Kerezoudis et al., 1995). Unfortunately, the potential contribution of α_2-adrenoceptors was not determined.

We believe that alterations in systemic arterial blood pressure had only a minimal impact on our regional blood flow results. For example, phentolamine caused more than 50% reduction of oral tissue vasoconstriction at a dose that produced only a modest, nonsignificant, systemic depressor effect (0.3 mg kg^{-1}). Similarly, prazosin produced significant reduction of evoked blood flow constriction in the lingual artery and gingival vasculature at the subdepressor 10 μg kg^{-1} dose. Finally, rauwolscine produced the entire dose-related blockade of tongue vasoconstriction without a significant systemic vascular action.

Innervation to the tongue is unique in that this organ receives both sympathetic vasoconstrictor *and* sympathetic, noncholinergic vasodilator fibers (Hellekant, 1976; Pleschka, 1984). For example, electrical stimulation of the sympathetic nerve trunk produces a marked decrease of blood flowing through the cat tongue that is reversed to an increase in flow after nonselective α-adrenoceptor blockade (Erici et al., 1952). This sympathetic vasodilation is not altered by administration of cholinergic agonists or antagonists. Using a plethysmographic technique in cats, Eccles and Wallis (1976) also demonstrated a clear reversal of sympathetic lingual vasoconstriction to a sympathetically mediated vasodilation after α-adrenoceptor antagonism with phentolamine.

In this study, we did not observe a consistent vasodilator pattern in any of the three measurement sites, either prior to, or after adrenoceptor blockade. The reason we did not observe a residual tongue vasodilator response after adrenoceptor receptor blockade is likely related to our technique used to measure lingual blood flow. For example, with the laser–Doppler technique, we are restricting our measurements to the more superficial vessels that may not be innervated by vasodilator fibers. In contrast, previous investigators used total lingual flow measurements or plethysmography, which reflect changes in total tongue blood flow. This would include both the mucosal and much larger muscular vascular beds.

In conclusion, oral tissue blood flows can be measured on a continuous basis using laser–Doppler (gingival and tongue surface) and ultrasonic flowmetry (lingual artery) techniques in anesthetized cats. Section of the ipsilateral cervical sympathetic nerve produced a modest increase of lingual arterial blood flow with no change in blood flow in the tongue surface or gingiva, suggesting differential degree of sympathetic neuronal tone to these vascular beds in cats. In the lingual artery and gingiva, sympathetic nerve stimulation caused frequency-dependent vasoconstrictor responses mediated by norepinephrine acting on a mixture of postjunctional α_1- and α_2-adrenoceptors. In contrast, the surface vasculature of the tongue responds to sympathetic nerve activation with vasoconstriction mediated primarily by activation of α_2-adrenoceptors.

Acknowledgements

This work was supported by a USPHS grant (EY 09344). The author thanks Ms. Linda Hess for technical assistance.

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