From:
The Department of
Pharmacology and
the Department of Endodontics,
Karolinska Institutet,
Stockholm, Sweden

THE EFFECT OF SYMPATHETIC NERVE STIMULATION ON THE RATE OF DISAPPEARANCE OF TRACERS FROM VARIOUS ORAL TISSUES

by
LENNART EDWALL
MAUD KINDLOVÁ

INTRODUCTION

Several observations indicate that the blood circulation in the oral tissues of mammals is influenced by nervous vasoconstrictor activity (*Tigerstedt*, 1923; *Taylor*, 1950; *Ogilvie, Gillilan & Knapp*, 1966; *Bishop & Dorman*, 1968). Using histological methods, sympathetic pathways could be traced in the alveolar nerves, including the nerves in dental pulp (*Christensen*, 1940); an adrenergic sympathetic innervation in the dental pulp was reported by *Anneroth* and *Norberg* (1968) and *Pohto* and *Antila* (1968). There is thus experimental evidence for a sympathetic vasoconstrictor control in the dental pulp and it seems probable that a similar control also exists in other oral tissues.

However, these studies have not provided information concerning the functional significance of the sympathetic influence, largely due to the fact that the methods used were not suitable for measuring graded responses to sympathetic stimulation (cf. *Bishop & Dorman*, 1968). Furthermore, it is not known whether there are any differences in the sympathetic nervous influence between various specific oral tissues, e.g. dental pulp and periodontal tissues.

By means of local tracer disappearance measurements (*Kety*, 1949) we have investigated the regional influence of sympathetic nerve activation

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on different vascular beds in the jaws of dog and cat. By graded electrical stimulation of the sympathetic nerve supply we wanted to obtain information about the range of vascular reactions following sympathetic nerve activation and also to see whether there are regional differences in these reactions.

A preliminary report of this investigation has been published previously (*Edwall*, 1968).

METHODS AND MATERIALS

Operative procedure

The experiments were performed on 39 dogs (6—27 kg) and on 13 cats (2.9—5.0 kg) anesthetized with sodium pentobarbital (30 mg/kg i.v. with supplement as necessary). The trachea was cannulated. Pressure in the femoral artery was measured by a Statham pressure transducer (P 23 AC) and recorded on a Rikadenki multichannel recorder or a Grass model 5 polygraph. The rectal temperature was continuously monitored and the body temperature was kept constant at 38°C by heating lamps. In the dog the cervical sympathetic trunk together with the vagus nerve was cut between the cranial and the caudal cervical ganglia (cf. *Mizeres*, 1955). In the cat the cervical sympathetic trunk was dissected free from the vagus nerve and transected, leaving the vagus intact. Sympathetic stimulation was performed in the cranial direction using a bipolar silver electrode with monophasic square wave pulses (1—4 msec, 4—10 V). Different stimulation frequencies were used and the order in which they were instituted was randomized.

Dihydroergotamine (Orstanorm,® Sandoz) 1 mg, and phentolamine (Regitin,® Ciba) 10 mg, injected via the cannulated cranial thyroid artery in the dog or lingual artery in the cat, were used to verify the nature of the vasomotor response in the oral tissues.

Radioactive tracers

The tracers were obtained in isotonic carrier-free solutions from AB Atomenergi, Studsvik, Nyköping, Sweden; Xe^{133} (5—16 μCi/μl) in saline solution, I^{125} and I^{131} (10—80 μCi/μl) as iodide dissolved in phosphate buffer (pH 7—8) containing sodium thiosulphate. I^{125} (1 μCi/μl), as 4-iodoantipyrine-I^{125}, was obtained from the same supplier in aqueous solution which was made isotonic by addition of saline immediately before each experiment.

Disappearance measurements in oral tissues in the dog

In the experiments on dog the head was immobilized by a stereotactic instrument and by insertion of dental acrylic between the jaws in the molar region. The tracer solutions (10—50μl) were injected with a Hamilton micro syringe, fixed in a stand; the injection time was 4—6 min. Four different locations of the tracer depot were used: 1) The interdental gingival papilla at the top of the bone septum in the premolar or molar regions (Gingiva). 2) The dental pulp of the canine or the first molar, via a channel drilled through the enamel and dentin (Pulp). 3) The periodontal membrane in the bifurcation of the first molar, via a channel drilled through the bottom of the pulp chamber (Periodontal membrane). 4) The movable submucosa on the buccal side of the alveolar process (Submucosa). The tracer depot was monitored by an external scintillation detector fed into two channels of scalers and digital printers.

For further technical details see *Bolme* and *Edwall* (1970). The measurements started immediately after the end of the injection and usually lasted for 2—3 hours. Three or four subsequent tracer injections could usually be made in the same animal. Radioactivity was counted for periods of 1 or 2 min.

Disappearance measurements in oral tissues in the cat

The disappearance of tracers from oral tissues of the cat was studied in a somewhat different way from that described above for the dog. The head was immobilized by means of a steel rod inserted between the jaws and secured in place by dental acrylic. The canine teeth remained exposed for cavity preparation and for insertion of a water circulated thermode in contact with one of them to insure maintenance of a constant temperature of 35—37°C; this was monitored by a thermocouple. A dentinal cavity was drilled with a carbide tipped endcutting bur rotated by a holder held between the fingers and observed through a binocular microscope. The preparation was kept wet with warm Macrodex® (Pharmacia) solution. The cavity was deepened until the pulp was visible through a thin layer of dentin. Preparations with pulp lesion were not included in this series of experiments. A volume of 0.1—0.2 μl of I^{125} solution was placed in the cavity, which was then covered with a thin plastic film to prevent evaporation and the depot was monitored externally (*Meyer*, 1966). Simultaneously, a depot of I^{131} solution, injected into the adjacent alveolar submucosa, was monitored by the same scintillation detector. For details concerning the double tracer technique, see *Bolme* and *Edwall* (1971).

Disappearance measurement in skeletal muscle

For comparison, the effect of sympathetic vasoconstriction on tracer disappearance was also studied in skeletal muscle. In 9 dogs and 6 cats a hind limb was immobilized by screws in the tibia and femur. The gastrocnemius-plantaris muscle was exposed. The ipsilateral lumbar sympathetic trunk, reached by a retroperitoneal approach, was transected. Stimulations at the level of L4—L5 were instituted in the peripheral direction using a bipolar silver electrode (0.1—2.0 msec, 4—8 V). Frequencies between 0.10 and 6 imp/sec were used. The radioactive tracer solutions were injected into the muscle in volumes of 0.04—0.10 ml during 1.5—4.0 min.

Calculations

After each run the total final background was determined (cf. *Odeblad, Westin & Englund*, 1959). The net pulse rate (gross pulse rate — background) was plotted semi-logarithmically against time. The disappearance rates were determined in two ways. In all cases the half-time of elimination (T 1/2 expressed in min) was determined graphically and then converted to the k-value using the formula: $k = 0.693/T\,1/2$; the k-value indicates the fractional elimination of the depot per min. In some experiments the disappearance rates were determined using the relation:

$k = (\log C_1 - \log C_2) / 0.4343\ (t_2 - t_1)$ (*Kety*, 1949).

C_1 and C_2 are the recorded net count rates of the depot at times t_1 and t_2; the time interval $t_2 - t_1$ is expressed in min. There was a good agreement between the two methods of analyzing the data.

Reduction in tracer disappearance rate (k %) was calculated from the expression: $k\,\% = 100 \cdot (k_{contr} - k_{stim}) / k_{contr}$, where k_{contr} and k_{stim} are the k-values during the preceding control period and the stimulation period, respectively.

RESULTS

Tracer disappearance measurements during resting conditions

In one series of experiments (10 dogs and 3 cats) the rate of disappearance was measured during resting conditions from tracer depots located in alveolar submucosa, gingiva, periodontal membrane or pulp.

In all cases where the tracer solution was injected into the tissue (25 depots), the disappearance curve was steepest during the first 5—60 min after the end of the injection; thereafter all the curves were monoexponential. By graphical resolution of the curve into exponential components (*Dobson &*

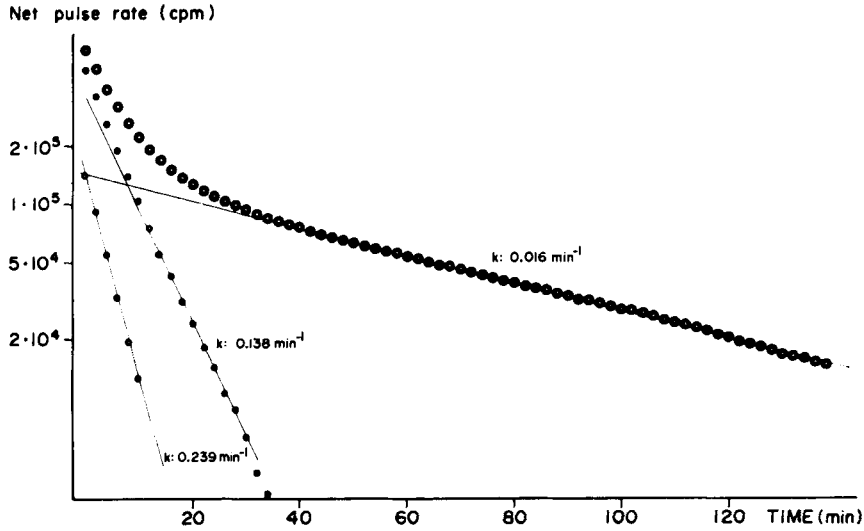

Fig. 1. Disappearance rate of a xenon depot injected into the buccal alveolar submucosa in cat. Large circles show net pulse rate. Small circles indicate the fast components obtained after graphical resolution. Resting conditions. Arterial pressure was constant during the experiment.

Warner, 1957) 2 or 3 components were obtained. A typical semilog plot of the disappearance rate of a xenon depot injected into the alveolar submucosa is shown in Fig. 1.

All the data have been analyzed by the graphical method. In order to be able to compare with another method of analysis, the data from 6 depots were also analyzed with the least square method on a computer. For each curve the two methods of analysis gave the same rates for the slowest component; the maximal difference between k-values obtained by the two methods was 5 % of the k-value. However, the methods did not give consistent results when calculating the faster components. Differences of up to 3 times the k-value were obtained.

Due to the small volume of the pulp of the cat it was not possible to inject tracer solution directly into the pulp without causing arrest of the pulpal blood circulation. Instead, the tracer was placed in a dentinal cavity. The resulting disappearance curves during resting conditions (4 depots) showed a steady monoexponential elimination rate for at least 50 min.

The disappearance rates from the various locations in the oral tissues did not differ significantly. The range of the means of k-values was 0.02—0.14 /min. Moreover, no differences could be detected in the k-values when different tracers were used.

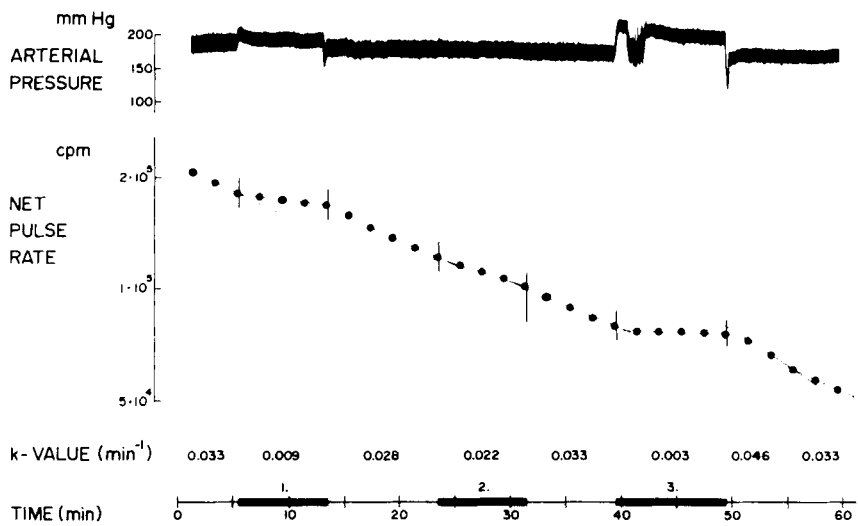

Fig. 2. Influence of sympathetic nerve stimulation on the disappearance rate of a xenon depot injected into the periodontal membrane in dog.
1. Stimulation with 9V, 4 msec, 2.5 imp/sec
2. Stimulation with 9V, 4 msec, 0.25 imp/sec
3. Stimulation with 9V, 4 msec, 6 imp/sec

Effect of sympathetic nerve stimulation

In all the depots investigated we observed a reduction in disappearance rate which was related to the frequency of stimulation. During recovery from maximal effects of stimulation transient overshoot of the k-values above control levels was observed. Fig. 2 shows a typical experiment in which a xenon depot was injected into the periodontal membrane. Stimulation at 2.5 imp/sec (Fig. 2:1) reduced the disappearance rate by about 75 %, while the subsequent low-frequency stimulation at 0.25 imp/sec (Fig. 2:2) induced a reduction of 20 %. Stimulation at 6 imp/sec (Fig. 2:3) reduced the disappearance rate by about 90 %. During the subsequent recovery there was a transient overshoot followed by a return to control values.

In Table I the relationship between stimulation frequency and k % in the different tissues of the dog is summarized. As can be seen, increases in frequency up to 2.5 imp/sec induced increasing responses in all the tissues studied. Maximal response was observed in the frequency range between 2.5 and 6 imp/sec. The level of maximal response was higher in the periodontal membrane than in the submucosa ($p<0.01$) and gingiva ($p<0.01$). In the pulp the responses showed a high variability. In the gastrocnemius muscle

Table I

Reduction of disappearance rate expressed as percentage change of k-value following sympathetic nerve stimulation with different frequencies. Dog. Mean, standard deviation (S.D.) and number of dogs (n) are shown. Tracers: Xe^{133} and 4-iodoantipyrine-I^{125}

Stim. freq. imp/sec	Submucosa Mean	S.D.	n	Gingiva Mean	S.D.	n	Period. membr. Mean	S.D.	n	Pulp Mean	S.D.	n	M. gastroc. Mean	S.D.	n
0.1	30	19	7	42	5	4	22	20	6	10	27	3			
0.25	35	13	11	40	8	4	30	8	6	21	21	2	27	12	6
1	54	13	7	64	7	5	54	7	5	31	17	3	64	15	6
2.5	68	14	14	67	8	5	75	10	7	71	25	4	65	23	6
3				68	—	1				54	—	1			
6	69	11	9	65	14	6	87	11	6	43	—	1	73	12	6
15	66	16	2	31	—	1									

the observed responses were of about the same magnitude as in the oral tissues. No difference could be observed between the responses following sympathetic stimulation when the different tracers were used.

A series of experiments was also performed on cats. Simultaneous measurements of disappearance from two depots, alveolar submucosa and dental pulp, were carried out. A representative experiment is shown in Fig. 3, where the effect on the disappearance rates of iodide from the pulp of the upper canine (I^{125}) and from the adjacent alveolar submucosa (I^{131}) was studied. Sympathetic nerve stimulation with 6 imp/sec (Fig. 3:1) reduced both k-values to zero during the second min. Partial recovery of the pulp k-value during the last minutes of stimulation was noted. After the stimulation period the pulp k-value rapidly rose to control level. The submucosa k-value approached zero during the last minute of stimulation and showed a less rapid recovery after the stimulation.

Stimulation with 10 imp/sec (Fig. 3:2) induced less marked initial reductions of both k-values than did the preceding stimulation. Prompt recovery of the pulp k-values was seen after the stimulation, while the recovery of the submucosa k-value was slower. As can be seen from this experiment, sympathetic nerve stimulation induced similar initial reductions in iodide k-values in the two tissues.

A consistent observation in the experiments on cats was a more rapid recovery from the sympathetic stimulation in the pulp than in the submucosa.

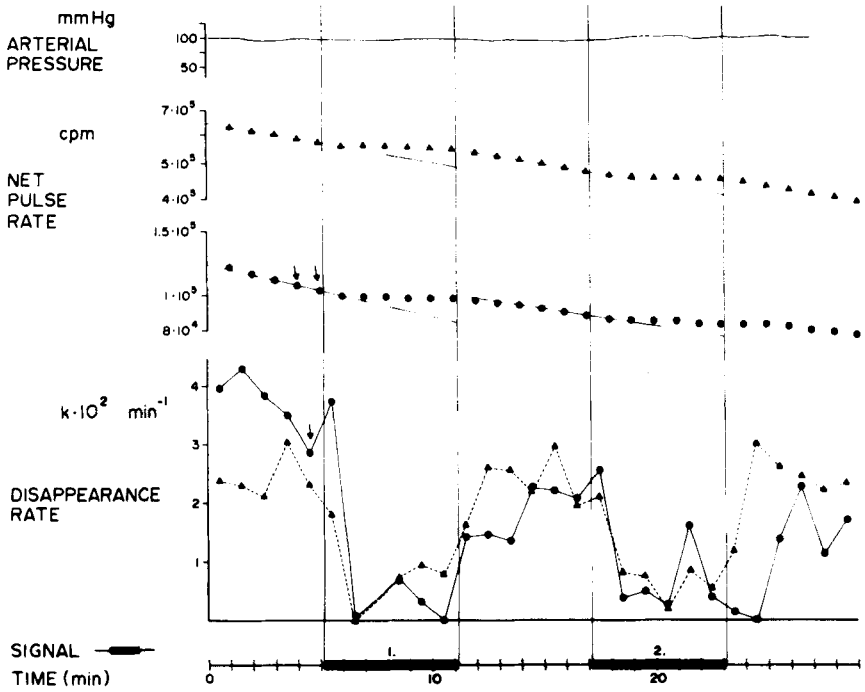

Fig. 3. Influence of sympathetic nerve stimulation on the disappearance rate of I^{125} from the pulp (▲) and of I^{131} from the submucosa (•) in cat. The monoexponential disappearance rate from the pulp had been observed for 16 min before the first stimulation. The control disappearance rate from the submucosa depot was not monoexponential.

1. Stimulation with 6V, 1 msec, 6 imp/sec
2. Stimulation with 6V, 1 msec, 10 imp/sec

Note that the disappearance rate is illustrated in two ways, both as a semilogarithmic plot of the net pulse rate of the depot against time and as k-values taken from the slopes between two consecutive readings. The k-value at the arrow was derived from the slope between the two points in the net pulse rate curve indicated with arrows. The k-values were calculated on a computer.

This difference was accentuated in old, mature animals, where a pronounced escape from the sympathetic vasoconstrictor influence was sometimes observed during the stimulation.

Fig. 4 summarizes the results from experiments on 7 cats where no escape was observed in the pulp k-values. For comparison, the results from intramuscular depots in the gastrocnemius muscle (6 cats) are included. In the oral tissues most stimulations were performed using frequencies between 2.5 and 10 imp/sec. No significant difference could be observed between the responses in the dental pulp and the submucosa. In both tissues the reduction

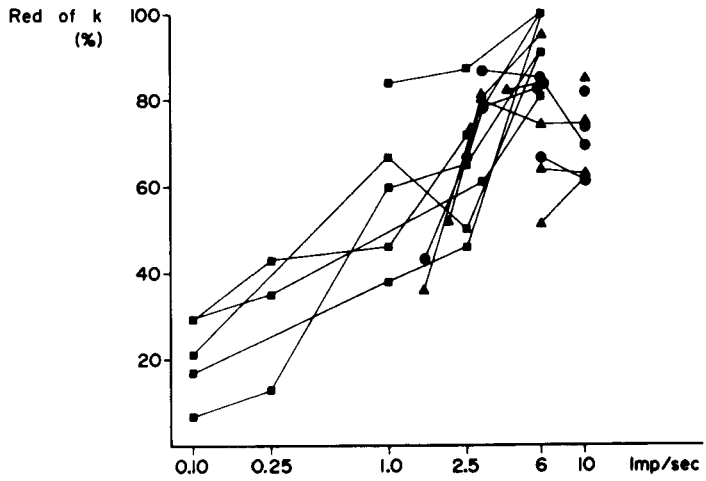

Fig. 4. Relation between frequency of sympathetic stimulation and reduction of k-value in per cent of control (k %). Dental pulp ▲. Alveolar submucosa ●. Gastrocnemius muscle ■. Tracers: I^{125} and I^{131}.Cat.

in disappearance rate was 76 %±5 % (mean ± S.E.) in the frequency range 2.5—10 imp/sec.

The *α*-receptor blocking agents dihydroergotamine or phentolamine were administered by close intra-arterial injection in 3 dogs and 2 cats. Complete blockade of the response to sympathetic stimulation in the pulp and the alveolar submucosa was observed in 2 dogs and both cats; partial blockade was obtained in the third dog. This indicates that the observed responses in the oral tissues were due to activation of sympathetic adrenergic nerves and receptors of the *α*-type.

DISCUSSION

In the present study the disappearance rate of locally injected diffusible tracers has been used as a means of measuring the effects of sympathetic nerve stimulation in various oral tissues. Regarding the localization of the tracer depots — it can be assumed that the injected tracer rapidly spreads by convection and diffusion to adjacent tissue (*Sejrsen*, 1969): a gingival depot would spread to the top of the interradicular bone septum and the periodontal membrane and similarly, a periodontal membrane depot may also be localized in the intraradicular bone septum. For the submucosal depots conditions are probably analogous.

Therefore it is reasonable to assume that the injected depot was localized in tissue with several parallel-coupled vascular beds with different perfusion rates, which could explain the initial composite shape of the disappearance curves (cf. *Dobson & Warner*, 1957). Furthermore, as a consequence of diffusion of the tracer between such vascular beds within the depot, a large number or a continuum, of exponential components in the disappearance rate can be expected (*Van Liew*, 1962; *Kjellmer et al.*, 1967). As was also shown by *Van Liew* (1962) such a multicomponent semilog curve after graphical resolution will appear to be a system of 2 or 3 components. This was also the case with all the composite curves in the present study. The observed discrepancy between the graphical and the least square analysis of the composite parts of the curves further supports the hypothesis that the composite part of the curves might be due to a multicomponent system.

However, the insult to the tissue induced by the injection needle and the injected volume is another factor determining the initial rate of disappearance (*Larsen, Lassen & Quaade*, 1966; *Tönnesen & Sejrsen*, 1970). Direct injection of tracer into the tooth pulp always resulted in an initial composite part of the disappearance curve, in spite of the fact that the depot was localized in one single type of tissue. On the other hand, the atraumatic application of tracer in a dentinal cavity consistently resulted in a monoexponential rate of removal (cf. *Sejrsen*, 1969).

A possible explanation of the latter finding would be the hypothetical existence of a rate limiting barrier for diffusion between the bottom of the dentinal cavity and the exchange vessels in the pulp. However, this explanation is unlikely, since no significant difference was found between the k-values obtained using the two methods to administer tracer to the pulp. Furthermore, in cases were lesions had been produced in the bottom of the dentinal cavity before the application of tracer, the resulting k-values did not differ from k-values of depots in cavities without lesion (*Edwall*, unpublished).

For these reasons it seems likely that the initial composite part of the disappearance curve following a direct local tracer injection is probably a result of the injection trauma and possibly also a consequence of inhomogeneity of tissue within the depot.

If inhomogeneity of tissue was of importance in the present study, which seems likely in the case of gingiva, periodontal membrane and submucosa, the rate of disappearance during the monoexponential part of the curve would reflect events in the least perfused parts of the tissue within the depot.

It is common practice to convert the disappearance data of lipid soluble tracers, such as xenon and iodoantipyrine, to blood flow expressed as ml/min/100 g tissue (*Tönnesen & Sejrsen*, 1970). However, in recent experiments on

the gastrocnemius muscle it could be shown that the disappearance rates of xenon and iodide were not only dependent on the blood flow but also influenced by local factors, presumably in the capillary section affecting the exchange function (*Bolme & Edwall*, 1971). Thus, activation of sympathetic vasoconstrictor nerves induced a greater reduction in tracer disappearance rate than in blood flow.

It is reasonable to assume that sympathetic nerve stimulation in the oral tissues induced a reduction in blood flow as well as a reduction in the capillary surface area and a change in the distribution of capillary blood flow. The latter factor could be of considerable importance if arterio-venous shunts exists in the pulp (*Provenza*, 1958; *Kramer*, 1960) and gingiva (*Staple & Copley*, 1959; *Forsslund*, 1959). Assuming a redistribution of blood flow from exchange vessels to shunt vessels during sympathetic vasoconstriction, a greater reduction of tracer disappearance rate than of blood flow would be expected (cf. *Hultén, Jodal & Lundgren*, 1969).

However, it seems more likely that the main effect of sympathetic nerve stimulation on the vascular bed in the pulp is a reduction of blood flow and capillary surface area, since vital microscopic studies of the cat pulpal vascular bed have shown a marked decrease in blood flow velocity and a vasoconstriction during sympathetic nerve stimulation (*Ogilvie, Gillilan & Knapp*, 1966; *Ogilvie*, 1967).

The maximal effects of sympathetic nerve stimulation on tracer disappearance rate in the oral tissues were obtained with frequencies of about 6 imp/sec. This rate of discharge of sympathetic vasomotor nerves seems to be within the physiological range (*Folkow*, 1952). At this frequency there was a 70—90 % reduction of the disappearance rate. Assuming a similar relationship between change in disappearance rate and blood flow as was found in skeletal muscle during sympathetic nerve stimulation (*Bolme & Edwall*, 1971) this would correspond to about 50—60 % reduction of total blood flow in the oral tissues.

There are very few studies reporting quantitative data for blood flow in oral tissues (cf. *Bishop & Dorman*, 1968). Using indicator fractionation techniques *Meyer, Weiner* and *Grim* (1964) and *Meyer* (1970) reported average blood flow values of 20—100 ml/min/100 g in different oral tissues. These values are unexpectedly high as compared with a rough estimate of the blood flow from the data in the present study; our data from experiments on dogs using xenon and iodoantipyrine indicate a resting blood flow of 2—14 ml/min/100 g which is within the range of blood flow for several other tissues (skeletal muscle, adipose tissue, skin, see *Mellander* and *Johansson*, 1968).

The weight of the isolated mandible in a 10 kg dog is usually less than 150 g. Assuming a high resting average blood flow of 10 ml/min/100 g in the mandible and a cardiac output of 3 l/min (*Meyer*, 1970) during resting conditions, a maximal sympathetic nerve stimulation to the mandible would result in a redistribution of less than 1 % of cardiac output. Obviously, such a redistribution is insignificant for the general circulatory homeostasis. It seems reasonable to assume that the marked influence of sympathetic nerve activation on the vascular beds in the oral tissues is only of local importance, e.g. for the function of the oral tissues.

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SUMMARY

The rate of disappearance of locally-injected diffusible tracers in different oral tissues in dog and cat has been used as a measure of the effects of sympathetic nerve stimulation. Tracers were administered to the pulp, gingiva, periodontal membrane and alveolar submucosa. Sympathetic nerve stimulation induced reductions of up to 70 % in tracer disappearance rate in all the oral tissues studied, with the exception of depots injected into the periodontal membrane, where the response was higher (about 90 % reduction). Sympathetic nerve stimulation in the oral tissues produced responses of the same order of magnitude as those obtained in skeletal (gastrocnemius) muscle using a similar technique.

RÉSUMÉ

ACTION DE LA STIMULATION DU SYMPATHIQUE SUR LA VITESSE DE DISPARITION DES TRACEURS DANS DIFFÉRENTS TISSUS DE LA CAVITÉ BUCCALE

La vitesse de disparition de traceurs diffusables injectés localement dans différents tissus oraux chez le chien et le chat, a été utilisée comme mesure des effets de stimulation sympathique. Les traceurs étaient injectés dans la pulpe, la gencive, le desmodonte ou la sous-muqueuse alvéolaire. La stimulation nerveuse sympathique réduisait d'environ 70 % la vitesse de disparition des traceurs dans tous les tissus oraux étudiés à l'exception des dépôts injectés dans le desmodonte pour laquelle la réduction atteignait 90 %. L'influence de la stimulation sympathique dans les tissus oraux semble

être du même ordre de grandeur que celle observée à l'aide d'une technique similaire, dans le cas du muscle squelettique (gastrocnémien).

ZUSAMMENFASSUNG

DER EINFLUSS SYMPATHISCHER NERVENREIZUNG AUF DEN ABTRANSPORT DER TRACERSUBSTANZEN IN VERSCHIEDENEN ORALEN GEWEBEN

Die Geschwindlichkeit des Abtransports von lokal injizierten diffusionsfähigen Tracersubstanzen wurde gemessen, um die Wirkungen sympatischer Nervenreizung in verschiedenen oralen Geweben des Hundes und der Katze zu bestimmen. Die Tracersubstanzen wurden in die Pulpa, Gingiva, periodontale Membran und alveoläre Submucosa injiziert. Eine maximale sympatische Nervenreizung im physiologischen Bereich verzögert die Geschwindlichkeit des Abtransport in allen untersuchten oralen Geweben um etwa 70 % mit Ausnahme von Depots, die in die periodontale Membran injiziert wurden, und in denen eine ungefähr 90 %-ige Verminderung zu beobachten war. Im Vergleich mit den Reaktionen, die man mit einer ähnlichen Technik im Skeletmuskel (Gastrocnemius) erhält, scheint der Einfluss sympatischer Nervenreizung in den oralen Geweben in der gleichen Grössenordnung zu sein.

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Address:
The Department of Pharmacology,
Karolinska Institutet,
Fack, 104 01 Stockholm 60, Sweden