Baroreceptor activity in muskrats (*Ondatra zibethica*) during nasal stimulation

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Received August 12, 1987

DOUSE, M. A., and JONES, D. R. 1988. Baroreceptor activity in muskrats (*Ondatra zibethica*) during nasal stimulation. Can. J. Zool. **66**: 2520–2527.

Nasal stimulation with water (simulated dive) in anesthetized muskrats (*Ondatra zibethica*) caused a significant increase in cardiac interval (209 ± 8 to 1370 ± 280 ms; mean ± SE) and decrease in mean arterial blood pressure (86 ± 8.6 mmHg to 75.7 ± 7.9 mmHg; 1 mmHg = 133.32 Pa). Baroreceptor activity, recorded from the peripheral end of a cut sinus nerve, stopped during the prolonged initial diastolic interval and in 3 of 10 fibres was absent for the first three heartbeats. Chemoreceptor activity did not change at the start of the nasal stimulation. As nasal stimulation continued, mean arterial blood pressure significantly increased (to 118.1 ± 9.5 mmHg), while cardiac interval decreased (to 740 ± 102 ms). This resulted in an increase in baroreceptor activity comparable with that seen during a similar increase in blood pressure in a pressor test. An increase in chemoreceptor activity also occurred during the latter part of nasal stimulation. Two types of efferent activity were recorded from the central end of a cut sinus nerve. One efferent responded to nasal stimulation with an immediate increase in neural activity, while activity of the other efferent halted. These responses would be expected to inhibit rather than foster baroreceptor activity in the intact nerve. The results suggest that there is no facilitation of the baroreflex engendered by changes at the receptor level that might contribute to the initiation of the dive bradycardia.

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Une stimulation nasale au moyen d'eau (plongée simulée) entraîne une augmentation significative de l'intervalle cardiaque (209 ± 8 à 1370 ± 280 ms; moyenne ± erreur type) et une diminution de la pression artérielle moyenne (86 ± 8,6 mmHg à 75,7 ± 7,9 mmHg; 1 mmHg = 133,32 Pa) chez des Rats-musqués (*Ondatra zibethica*) anesthésiés. L'activité baroréceptrice, enregistrée à l'extrémité périphérique d'un nerf sectionné du sinus cesse au cours de l'intervalle diastolique initial prolongé et elle s'est avérée nulle en 3 trois des 10 fibres au cours des trois premiers battements cardiaques pendant au essai. L'activité chimioréceptrice ne change pas au début de la stimulation nasale. Plus tard au cours de la stimulation, la pression arterielle moyenne augmente significativement (à 118,1 ± 9,5 mmHg), alors que l'intervalle cardiaque diminue (à 740 ± 102 ms). Ce phénomène entraîne une augmentation de l'activité baroréceptrice comparable à l'augmentation de la pression sanguine qui se produit au cours d'un test vaso-presseur. Il se produit aussi une augmentation de l'activité chimioréceptrice à la fin de la stimulation nasale. Deux types d'activité efférente ont été reconnus à l'extrémité centrale d'un nerf sectionné du sinus. L'un des efférents réagit à la stimulation nasale par une augmentation immédiate de l'activité neurale, alors que l'activité de l'autre efférent est enrayée. Ces réactions devraient semble-t-il inhiber l'activité baroréceptrice du nerf intact plutôt que de la stimuler. Les résultats indiquent que les changements au niveau des recepteurs n'entraînent pas de facilitation du baroréflexe, ce qui pourrait contribuer au déclenchement de la bradycardie de plongée.

[Traduit par la revue]

Introduction

During forced submergence, mammals invoke a series of respiratory and cardiovascular reflexes collectively called the diving response. This response is characterized by apnea, a decrease in cardiac output, and an increase in peripheral resistance. The result is a redistribution of blood flow away from the muscles and splanchnic beds to the heart and brain. The diving response is viewed as an oxygen conserving mechanism that preserves the integrity of the obligate aerobic tissues during the prolonged period of apnea accompanying submergence.

The initiation of the dive response in mammals is primarily the result of stimulation of nasal receptors by water (Angell James and Daly 1972; Drummond and Jones 1979; Dykes 1974). In addition, barorceptors acting via the baroreflex may be involved in the initiation (Angell James *et al.* 1978; Daly 1984) as well as the maintenance of the response (Blix and Folkow 1983; Butler and Jones 1982). Baroreceptor involvement in the dive bradycardia may be through an increase in baroreflex sensitivity (Angell James *et al.* 1978), occurring either in the brainstem or at the receptor site. The neural activity of the carotid sinus baroreceptors *per se* may be altered in several ways. The threshold and sensitivity of the baroreceptors may be modified during nasal stimulation in both the short and long term by efferent activity (Majcherczyk *et al.* 1980; Tomomatsu and Nishi 1981). In addition to a sympathetic innervation from the superior cervical ganglion to the sinus area, the sinus nerve itself contains efferents. In mammals, the sinus nerve efferents are a rhythmical, respiratory-modulated discharge of sympathetic origin (Biscoe and Sampson 1968) as well as randomly discharging fibres that innervate the chemoreceptors (Neil and O'Regan 1971; Sampson and Biscoe 1970) and possibly also the baroreceptors (Koushanpour and Behnia 1982). This innervation has the potential to substantially alter receptor discharge. Also, in the long term, levels of circulating catecholamines increase during nasal stimulation (Allison and Powis 1971; Hance *et al.* 1982; H. J. Mangalam and D. R. Jones, unpublished observation) and may alter receptor discharge through their effects on vessel wall stiffness or on the receptors themselves (Aars 1971; Tomomatsu and Nishi 1981).

Baroreceptor activity has never been recorded in a diving mammal during submergence, although much has been made of their role in the diving response. Hence, the objective of the

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Printed in Canada / Imprimé au Canada

present investigation was to examine carotid sinus neural activity before and during nasal stimulation in the anesthetized muskrat (*Ondatra zibethica*). Unfortunately, we were unable to record afferent activity from nerve slips isolated from otherwise intact sinus nerves, so these activities were recorded from the peripheral end of the cut sinus nerve. We felt that changes in afferent baroreceptor neural activity alone could give us some idea of the role of the baroreflex in cardiovascular adjustments during nasal stimulation. Additionally, the effects of the intact superior cervical ganglion innervation to the sinus area, as well as humoral or mechanical effects on baroreceptor output during nasal stimulation, could be assessed by comparing baroreceptor activity before and during a simulated dive. Finally, in a limited series of experiments, efferent sinus activity was recorded from the central end of the cut sinus nerve to establish that types of efferent activity common in mammals existed in muskrats. Furthermore, changes in efferent neural activity during nasal stimulation allowed us to estimate, from information obtained in nondiving mammals, what effects these changes might have on baroreceptor discharge in muskrats with intact sinus nerves.

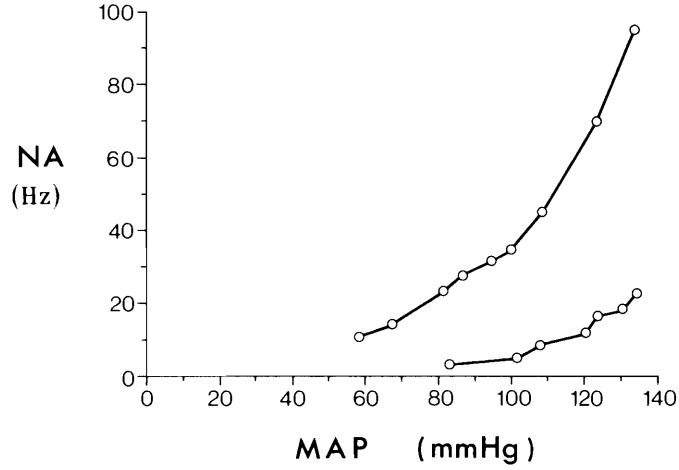

FIG. 1. The effect of changing mean arterial blood pressure (MAP) on the neural activity (NA) of two single-fibre baroreceptor afferents recorded from the peripheral end of the cut sinus nerve. At the mean pressures, indicated by the open circles, the total number of nerve impulses was counted during three heartbeats and the number was converted to Hz.

Methods

Experiments were done on 16 muskrats (*Ondatra zibethica*) of both sexes, varying in mass from 0.548 to 1.124 kg. Muskrats were obtained from commercial trappers operating in the lower mainland area of British Columbia. The animals were anesthetized with urethane (ethyl carbamate, 1000 mg·kg^{-1}, BDH Chemicals Canada Ltd., Vancouver, B.C.) or with a combination of fentanyl and droperidol (Innovar, 0.25 mL·kg^{-1}, Janssen Pharmaceutica, Mississauga, Ont.) and thiopental sodium (Pentothal, 20 mg·kg^{-1}, Abbott Laboratories Ltd., Montreal, Que.) injected intraperitoneally, after prior induction with ethyl ether. The latter combination of drugs resulted in a light level of anesthesia and therefore, initially and periodically throughout the experiment, all incisions were infiltrated with local anesthetic (Xylocaine, 2%, Astra Pharmaceutical Canada Ltd., Mississauga, Ont.) Further anesthetic agents were administered as required. After anesthesia the muskrat was placed on its back and the trachea was cannulated low in the neck with two cannulae, one facing the oral cavity and the other the lungs. The muskrats were then paralyzed with *d*-tubocurare (Tubarine, 0.2 mg·kg^{-1}, Burroughs Welcome Inc., Kirkland, Que.). Ventilation with humidified room air, supplemented with oxygen when necessary, was carried out with a positive pressure pump at a frequency of 70 breaths/min. End expiratory pressure was set at approximately 5 cmH_2O and maximum inspiratory pressure did not exceed 15 cm H_2O. Intratracheal pressure was monitored with a Statham P23V pressure transducer. Rectal temperature was monitored and maintained at 37°C by means of a heating pad, with additional radiant heat when necessary. At the end of the experiments the animal was killed by an overdose of thiopental sodium, i.a.

Both femoral arteries were cannulated with polyethylene tubing (i.d. = 0.58 mm, o.d. = 0.965 mm). One cannula was attached to a Biotec BT70 pressure transducer for continuous measurement of arterial blood pressure while the other cannula was attached to a saline–phenylephrine reservoir (Neo-Synephrine, 0.04 mg·mL^{-1}, Winthrop, Aurora, Ont.) with a pressure head of 67 cmH_2O. If arterial pressure dropped below 67 cmH_2O, then the reservoir system drained into the artery, increasing arterial constriction and maintaining blood pressure. The reservoir system was closed before and during experimental tests.

The left carotid bifurcation was exposed by sectioning the esophagus and retracting it in the midline. The left carotid sinus nerve was identified, isolated, and cut at its junction with the glossopharyngeal nerve when recording receptor activity, or cut as it joined the carotid bifurcation when recording efferent activity. The right carotid sinus nerve and both aortic nerves were left intact. The cut nerve was laid on a small metal plate and dissected in a pool of warm liquid paraffin (37°C). Activity from small filaments was recorded with bipolar silver electrodes, amplified (Framp Pra-1, F.M. Smith, Vancouver, B.C.), and monitored on an oscilloscope (Tektronix 5113, Beaverton, OR). The activity from single- or few-fibre preparations was used to trigger a window discriminator (World Precision Instruments Inc., New Haven, CT). Pulses from the window discriminator were then counted by a ratemeter. Arterial blood pressure and respiratory pressure, or arterial pressure and nerve discharge frequency were displayed on a Brush 220 (Gould Inc., Cleveland, OH) chart recorder. Arterial blood pressure, respiratory pressure, and the unfiltered neural activity were also recorded on magnetic tape (Tanberg, TIR 115, Oslo, Norway).

The carotid baroreceptors were identified by the relation of their discharge concurrent with blood pressure pulses and cessation of activity upon occlusion of the left common carotid artery. The response of carotid baroreceptors to changes in arterial blood pressure was determined by the slow infusion of phenylephrine (0.35 mg·kg^{-1}) or papaverine (Papaverine hydrochloride, Frosst, 4.0 mg·kg^{-1}). Mean arterial blood pressure versus baroreceptor activity response curves were then constructed. Mean arterial pressure was used as the independent variable, as it has the best correlation with baroreceptor activity and function (Landgren 1952; Arndt *et al.* 1977). Baroreceptor activity was also monitored during a pressor test, where an increase in blood pressure was induced by a rapid injection of phenylephrine (0.35 mg·kg^{-1}, i.a.). Phenylephrine has minimal direct cardiac effects, as well as minimal effects on the baroreceptors themselves (Faris *et al.* 1980; Peveler *et al.* 1983). Nerve discharges from carotid body chemoreceptors were identified by their sporadic random discharge and their prompt increase in activity when the muskrats were ventilated with 100% nitrogen. The response of the chemoreceptors to changes in blood oxygen tensions was determined by ventilation of the muskrat with different gas mixtures. Fraction of inspired oxygen versus chemoreceptor activity response curves were then constructed.

In both cases, afferent neural activity was monitored before and during simulated dives induced by nasal stimulation while simultaneously stopping the respirator with the lungs deflated. Stimulation of nasal receptors was achieved by passing water through the nasally directed cannula and out of the nares at a flow rate of 150 mL·min^{-1}. Nasal stimulation was stopped when the cardiac interval was approximately twice the prestimulation level or a period of 2 min had elapsed, whichever came first. This resulted in a mean nasal stimulation dura-

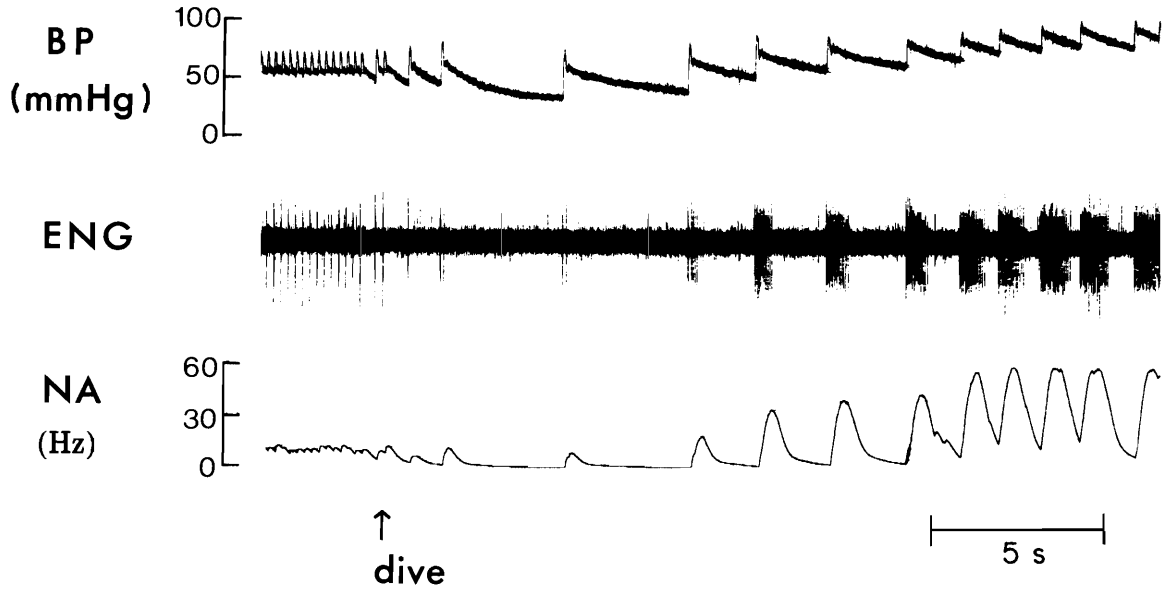

FIG. 2. Effect of nasal stimulation with water on arterial blood pressure (BP) and baroreceptor activity. ENG, electroneurogram of a single baroreceptor; NA, baroreceptor activity. Water stimulation ("dive") was initiated at the arrow.

tion of 52.7 ± 31.7 s (mean ± SD). In this paper the terms nasal stimulation and dive are used synonymously.

Efferent activity was recorded from the central end of the cut sinus nerve in four muskrats. The effect on efferent activity of increases (1.0 mg·kg^{-1} phenylephrine i.a.) and decreases (5.0 mg·kg^{-1} papaverine i.a.) in blood pressure as well as changes in the frequency of the artificial ventilation were monitored. In addition, efferent neural activity was recorded before and during nasal stimulation.

Mean arterial blood pressure (MAP) was calculated from the blood pressure trace using the formula MAP = $(2D + S)/3$, where D is diastolic blood pressure and S is systolic pressure. Cardiac intervals (CI) were also measured from the blood pressure trace as the mean of three consecutive intervals in all pretest, test, predive, start of dive, and end-dive situations. Ventilation frequency was measured from the respiratory pressure trace and calculated as the mean of three consecutive intervals, then converted to breaths/min. For data analysis, the total number of impulses during three heartbeats was counted, 10 s before and for the first three and last three CIs of a period of nasal stimulation. In pressor tests, impulses were averaged over three heartbeats before the test and at the peak of the pressure response. These values were converted into hertz (Hz). Impulses per heartbeat were obtained by dividing impulses per second by the mean CI of the three appropriate heartbeats. However, chemoreceptor response curves were done by counting the total number of impulses in 1 min, for any given gas mixture, and then expressed as Hz.

Values in the text are given as means ± SEM, unless otherwise noted. Tests for significant differences were carried out using analysis of variance for repeated measures over time in the case of the arterial blood pressure and cardiac interval response to nasal stimulation. A two-way analysis of variance was used to compare mean arterial pressure and cardiac interval responses to pressor tests with responses to nasal stimulations. In the case of a significant F value, paired comparison of means was done with Scheffé's test. Paired t-tests were used to compare neural activity before with that after a test or nasal stimulation. $P < 0.05$ was taken as the fiducial limit of significance in all statistical tests.

Results

Baroreceptor afferent activity before and during nasal stimulation

Neural activity of a total of 10 single-fibre baroreceptors was recorded from 10 muskrats. Changing MAP by slow infusion of pressor and depressor drugs caused changes in receptor activity (Fig. 1). The fibre on the left in Fig. 1 had a threshold pressure of 58.0 mmHg and a frequency response of 95 Hz at the maximum pressure attained, 130.0 mmHg. The fibre on the right had a higher threshold of 83.0 mmHg, and a lower discharge frequency of 20 Hz at a pressure of 135.0 mmHg (Fig. 1). The frequency response curves of the other baroreceptors were similar to one or the other of these representative curves.

Baroreceptor recordings were also obtained from five muskrats during a pressor test. Injecting 0.35 mg·kg^{-1} phenylephrine resulted in a significant increase in MAP (from 84.6 ± 13.7 mmHg to 149.0 ± 8.0 mmHg) and CI (from 208 ± 8 ms to 452 ± 109 ms). Concurrent with the increase in MAP, arterial baroreceptor activity increased significantly from 10.4 ± 3.2 to 40.4 ± 11.9 Hz at peak pressure.

Running water through the nares resulted in an immediate lengthening of CI (from 209 ± 8.0 ms predive to 1370 ± 280 ms) and a decrease in MAP (from 86.0 ± 8.6 mmHg predive to 75.7 ± 7.9 mmHg). Baroreceptor discharge ceased for a period of time equal to that of the greatly lengthened initial CI of the nasal stimulation (Fig. 2). Three of the 10 fibres were silent for the first three heartbeats, but in the others there was a burst of activity with each subsequent pressure pulse. These bursts became successively larger as the mean arterial pressure slowly increased during nasal stimulation. At the onset of nasal stimulation, baroreceptor discharge during the initial three CIs was unchanged (8.4 ± 2.8 Hz) compared with predive (11.9 ± 2.8 Hz). By the end of nasal stimulation, MAP, CI, and baroreceptor discharge were significantly above predive levels (118.1 ± 9.5 mmHg, 740 ± 102 ms, and 37.6 ± 6.3 Hz, respectively). An increase in activity was seen in all the receptors, although it was somewhat attenuated in high threshold, low frequency response fibres (Fig. 3A).

A two-way analysis of variance for CI and MAP changes of the five muskrats tested in both the pressor test and nasal stimulation showed no significant difference between the pretest and predive CIs and MAPs. As well, there was no significant difference between the pressor test and the end-dive CIs

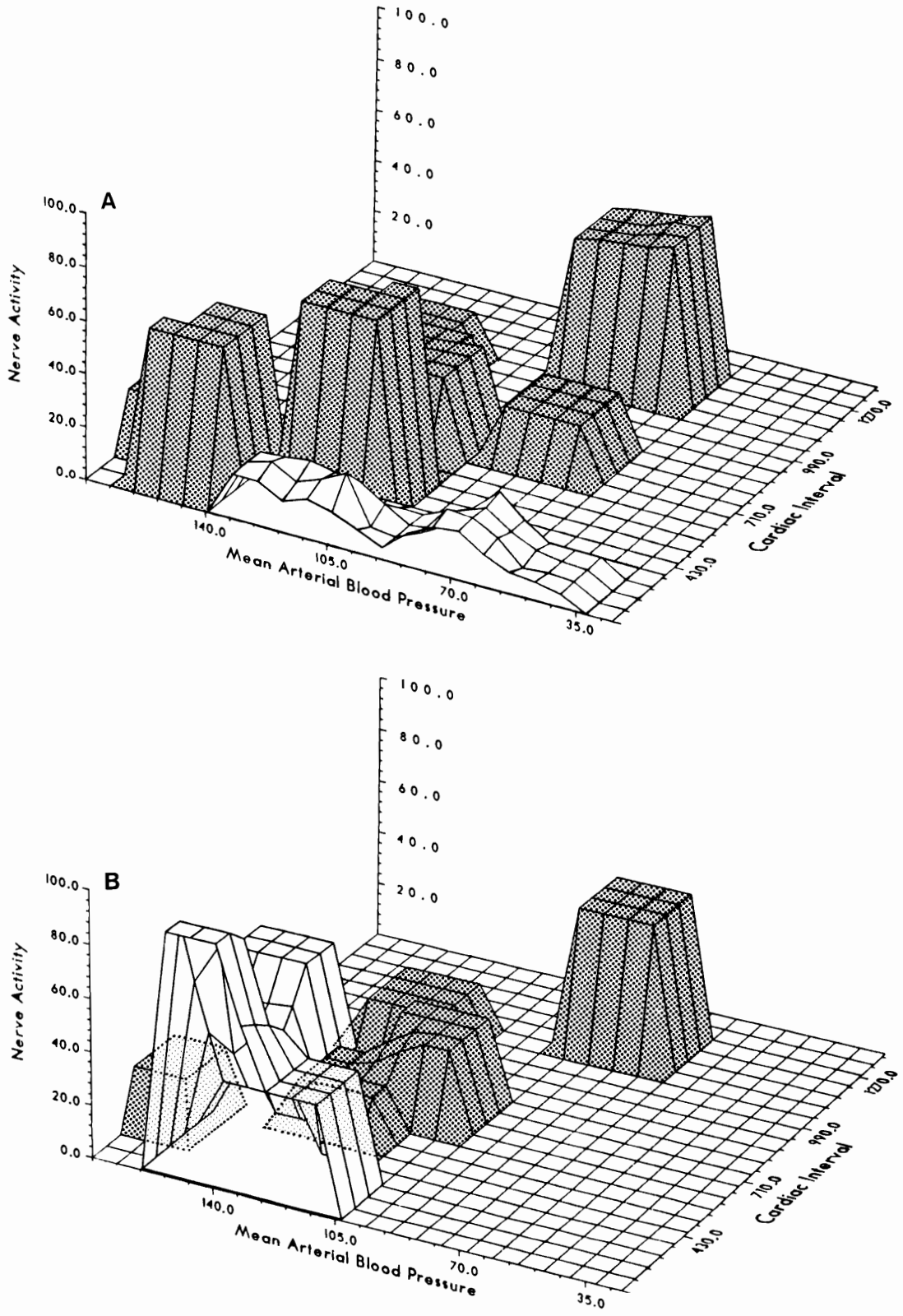

FIG. 3. (A) The effect of nasal stimulation with water on baroreceptor discharge. The open surfaces represent the output of 10 single fibres before nasal stimulation and the stippled surfaces the output of the same fibres at the end of nasal stimulation. (B) A comparison between baroreceptor discharge, in five single fibres, during a pressor test (open surfaces) and in the same five fibres at the end of a period of nasal stimulation (stippled surfaces). Both A and B are three dimensional plots of neural activity (Hz) in response to changes in mean arterial blood pressure (mmHg) and cardiac interval (ms).

and MAPs. However, in both the pressor test and during maintained nasal stimulation there was a significant increase in CI and MAP. Baroreceptor activity increased significantly in the pressor test and at end-dive, compared with pretest and predive values, although maximum baroreceptor activity in the pressor test (40.4 ± 11.9 Hz) was not significantly different from that at end-dive (27.6 ± 6.3 Hz). Furthermore, the number of impulses per heartbeat at the peak pressure in the pressor test (15 ± 4 per heartbeat) was not significantly different from the end-dive number (24 ± 9 per heartbeat). Visual confirmation of this is shown in Fig. 3B, in which nerve discharge is plotted against MAP and CI. Nerve discharge in pressor and nasal stimulation tests overlap in the same ranges of MAP and CI (Fig. 3B).

Other afferent activity

Two recordings of chemoreceptor activity were obtained, one each from two muskrats. One recording consisted of single-fibre activity, while the other recording was of a few-fibre preparation. Changing the level of inspired oxygen caused changes in receptor activity, resulting in the response curve shown in Fig. 4. Flowing water through the nares of the muskrat had no initial affect on chemoreceptor activity (Fig. 5). As nasal stimulation progressed, chemoreceptor activity gradually increased. At the termination of nasal stimulation, chemoreceptor activity had increased by 1.6 to 2.0 times that before stimulation (Fig. 5).

Efferent neural activity and its modulation by nasal stimulation

Two types of efferent activity were recorded from the cut central end of the carotid sinus nerve. One recording from one muskrat was of a single fibre that displayed a random, nonrhythmical discharge. Three recordings of few-fibre activity were recorded from three muskrats that had a rhythmical discharge pattern. The peak discharge rate of these latter efferents varied considerably from preparation to preparation, but the rhythmical activity was consistent and coincided with the respiratory pump frequency (Fig. 6A). Changes in the respiratory pump frequency, over the range 20–75 breaths/min, resulted in the same change in the rate of cyclic activity of the rhythmic efferents. An increase (+33.8 ± 8.3 mmHg) or decrease (−38.5 ± 7.3 mmHg) in arterial blood pressure had no effect either on the peak discharge rate, or on the rate of cyclic activity, of the rhythmic efferents. Running water past the nares of the muskrats, at the same time as stopping ventilation with the lungs deflated, resulted in efferent activity stopping for 4.5, 25.9, and 51.6 s for each efferent (Fig. 6A).

The neural activity of the single, randomly discharging efferent was not affected by a decrease in arterial blood pressure (−33.0 mmHg), but responded to an increase in blood pressure (+55.0 mmHg) with a burst of activity after a latent period of 22.5 s. There was no response by this efferent to changes in ventilation frequency. Running water through the nares of the muskrat resulted in an immediate increase in the activity of this nerve. The activity reached a peak discharge rate of 24 Hz and continued for a time period of 6.6 s, whereupon the discharge rate returned to prestimulation values and remained there for the duration of the nasal stimulation (Fig. 6B).

Discussion

In muskrats, nasal stimulation with water resulted in a tremendous increase in the cardiac interval. Arterial blood pressure initially decreased, but by the end of the test had significantly increased over prestimulation levels. This increase in blood pressure, in the face of a decrease in cardiac output, is assumed to be indicative of a major sympathetic vasoconstriction of the periphery. These responses are similar to those observed by previous authors studying this species (Drummond and Jones 1979; Jones *et al.* 1982). Nasal stimulation in anesthetized muskrats is also characterized by a lack of central respiratory output (Drummond and Jones 1979; P. C. Drummond and D. R. Jones, unpublished observations). In our study, a central apnea was also assumed to occur during nasal stimulation. This is supported by the lack of rhythmical, respiratory modulated efferent sinus nerve activity during nasal stimulation.

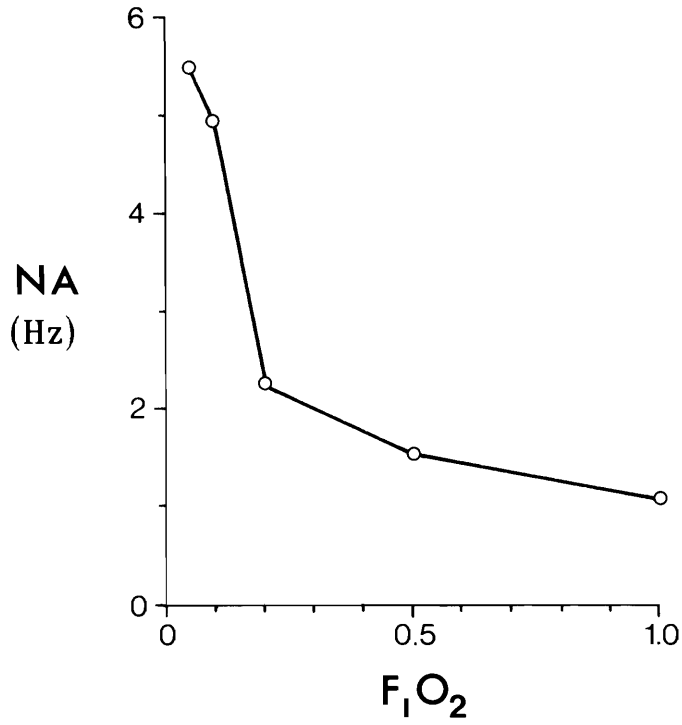

FIG. 4. The effect of changing the fraction of inspired oxygen FI_{O_2} on the neural activity (NA) of the single-fibre chemoreceptor recorded from the peripheral end of a cut sinus nerve.

The baroreceptor activity versus blood pressure response curves showed a trend for a dichotomy in fibre types, either a low-threshold, high-frequency response or a high-threshold, low-frequency response was observed. This is typical of mammalian baroreceptors (Kirchheim 1976). Initially, baroreceptor activity during nasal stimulation decreased to zero for a period of time corresponding to the greatly lengthened cardiac interval. In three fibres there was no discharge, even during systole, for the first three heartbeats after the start of nasal stimulation. As arterial blood pressure rose during nasal stimulation, the baroreceptor activity increased to levels exceeding prestimulation values. The increase in baroreceptor activity by the end of nasal stimulation was comparable to that seen for a similar increase in mean blood pressure in the pressor test. This suggests that baroreceptor activity was not being modified by any effects of the dive response on threshold or sensitivity at the receptor site *per se*. Thus, any changes in sympathetic activity from the superior cervical ganglion or increase in the levels of circulating catecholamines, which is known to occur during both nasal stimulation and enforced dives (Allison and Powis 1971; Hance *et al.* 1982; H. J. Mangalam and D. R.

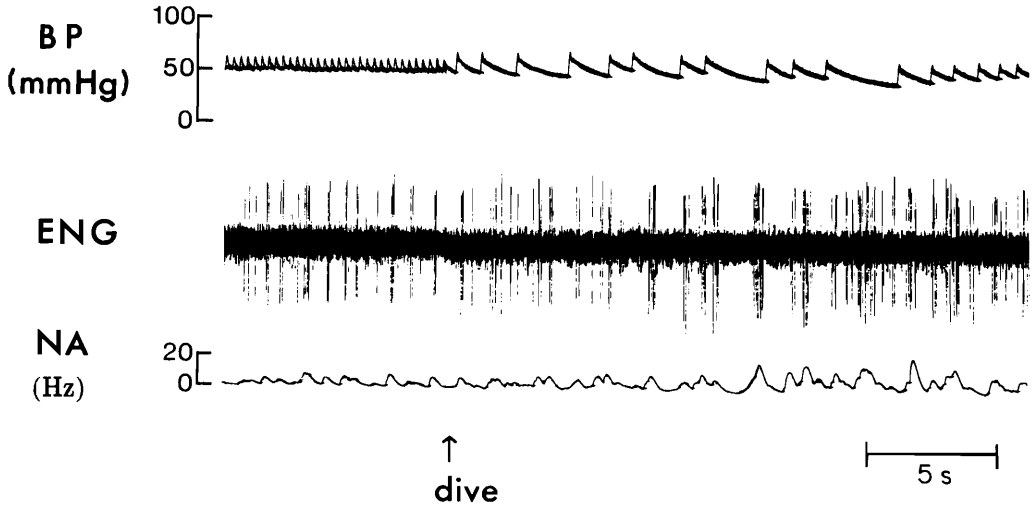

FIG. 5. Effect of nasal stimulation with water on arterial blood pressure (BP) and chemoreceptor activity. ENG, electroneurogram of a single-fibre chemoreceptor; NA, chemoreceptor activity. Water stimulation ("dive") was initiated at the arrow.

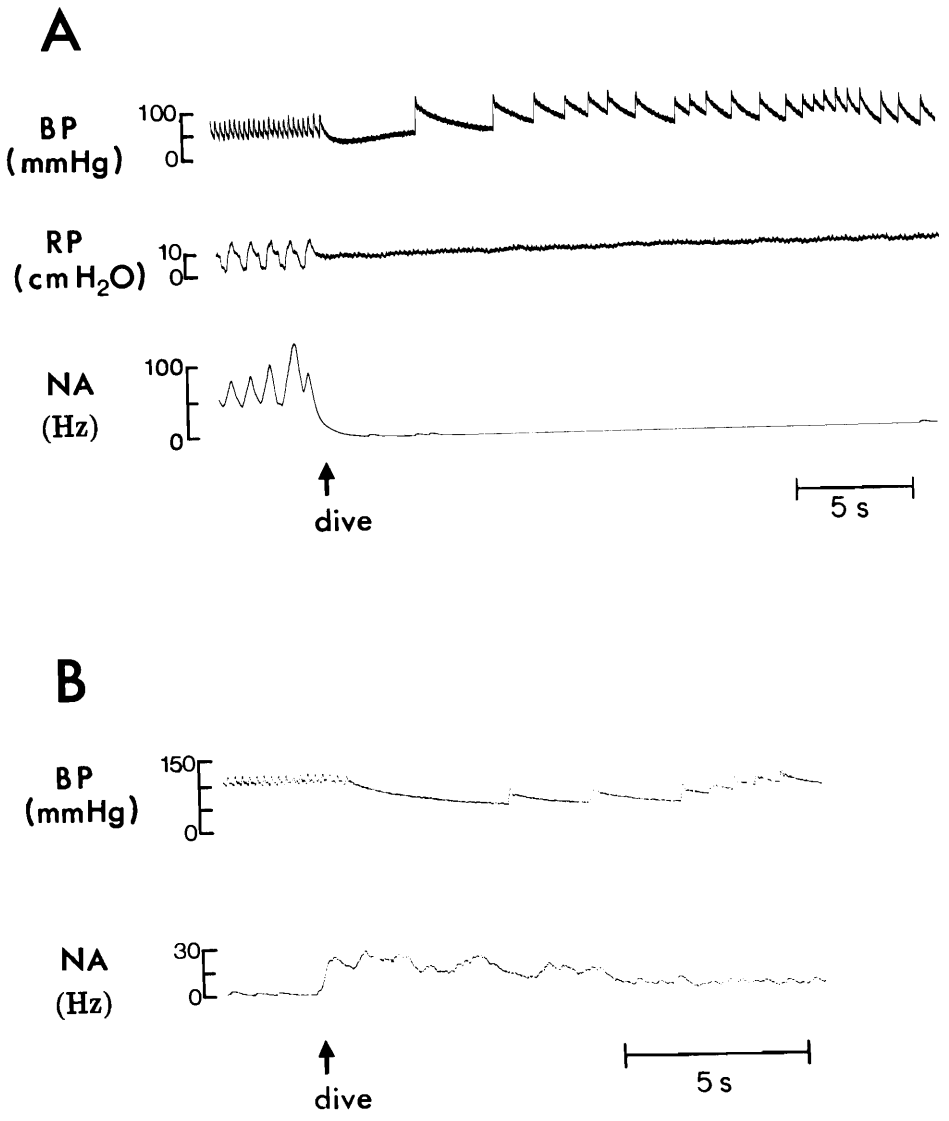

FIG. 6. (A) Effect of nasal stimulation with water and stopping artificial ventilation in the expiratory phase (RP, respiratory pressure) on arterial blood pressure (BP) and neural activity (NA) of a few-fibre preparation of rhythmic efferents recorded from the central end of the cut sinus nerve. (B) Effect of nasal stimulation with water on arterial blood pressure (BP) and neural activity (NA) of a single-fibre, randomly discharging efferent. In both A and B, water stimulation ("dive") was initiated at the arrow.

Jones, unpublished observations), had no effect on neural activity of the baroreceptors.

Unfortunately, the carotid sinus nerve was cut to record the baroreceptor response to nasal stimulation, removing any possible influence by the dual innervation of efferent fibres in the nerve. Nonrhythmical efferents have been proposed to be inhibitory to the baroreceptors (Koushanpour and Behnia 1982) while rhythmic sympathetic efferents are predominantly excitatory to the baroreceptors (Eyzaguirre and Lewin 1961; Floyd and Neil 1952; Koizumi *et al.* 1971). Flowing water past the nares of the muskrats resulted in an immediate halt in the rhythmic efferent activities and an increase in activity in the nonrhythmical efferent. Thus, the net effect, if any, of the carotid sinus efferents during the initial phase of nasal stimulation would be to decrease baroreceptor activity.

The reduced, or unchanged, baroreceptor activity upon initiation of nasal stimulation is in contrast to the increase in receptor activity that would be expected if potentiation of the baroreflex occurred at the receptor level. Furthermore, an increase in the central brainstem sensitivity of the baroreflex is unlikely to contribute to the cardioinhibitory response initiated by nasal stimulation; in three animals there was no baroreceptor input in the recorded nerve and presumably none in the intact contralateral carotid sinus nerve by which the baroreflex could be activated. Therefore, there would be no contribution by the baroreceptors to the lengthening of the initial cardiac intervals. In fact, the lack of baroreceptor activity would tend to oppose bradycardia, although an increase in peripheral vasoconstriction would be facilitated.

Although we only obtained recordings from two animals, the chemoreceptor response curves were typical of mammalian peripheral chemoreceptors, with the base of the curve centered at normal oxygen levels (Hornbein *et al.* 1961; Biscoe *et al.* 1967). There was no increase in the neural activity of the chemoreceptors during the initial phase of nasal stimulation, and *in vivo* there may be an inhibition of chemoreceptor activity due to the activity of the carotid sinus efferents (McDonald 1981; Neil and O'Regan 1971; O'Regan 1981; Sampson and Biscoe 1970). As nasal stimulation continued, the chemoreceptors responded with a slow erratic increase in activity. Hence, despite the small sample size, there is probably no potentiation of the chemoreflex at the receptor level, at least at the start of nasal stimulation. Our study does not exclude an increase in brainstem sensitivity that facilitates the primary cardioinhibitory chemoreflex (Angell James and Daly 1972, 1973; Elsner *et al.* 1977), but there is some doubt as to whether or not an interaction of this type actually occurs (Butler and Jones 1982).

Acknowledgements

This work was supported by grants from the British Columbia Heart Foundation and the Natural Sciences and Engineering Research Council of Canada. We are grateful to Dr. Richard Stephenson and Dr. Frank Smith for their comments on an earlier draft of the manuscript.

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