REVISTA ESPAÑOLA DE FISIOLOGIA, 32, 239-248, 1976

Effects of Sympathetic Stimulation on Carotid and Aortic Baroreceptors in the Cat

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(Received on February 10, 1976)

J. SIMON, J. L. ZAMORANO, J. YAJEYA and C. BELMONTE: *Effects of Sympathetic Stimulation on Carotid and Aortic Baroreceptors in the Cat.* Rev. esp. Fisiol., 32, 239-248. 1976.

Variations in the discharge of baroreceptor units in the left aortic nerve were investigated during stimulation of the stellate ganglion both in the intact cat and *in vitro* perfusion of the aortic arch. The effects of stimulation of the peripheral cervical sympathetic trunk of the baroreceptor discharge in the carotid nerve during *in vitro* perfusion of the carotid artery were further studied. Stimulation of the stellate ganglion or the aortic nerve in the intact cat caused a simultaneous increase in arterial pressure, heart rate and number of baroreceptor impulses in a filament to the left aortic nerve. In the *in vitro* studies, decreases in the number of baroreceptor impulses both in the aortic and carotid nerves were produced in most cases during the stimulation of the sympathetic nerves. These effects were only observed during low pressure perfusion of the isolated artery and in low frequency changes. The infusion of norepinephrine caused a more marked decrease.

The sensory input of some mechanoreceptors can be modified by electrical stimulation of local sympathetic fibers (9, 15, 17). In baroreceptors small changes in the frequency of impulses occur after local application of catecholamines on the carotid and aortic sinus wall (1, 14). Similar variations in the frequency of carotid baroreceptor impulses have been observed during electrical stimulation of sympathetic fibers inervating the carotid sinus in cats (5, 19) and Virginia opossum (12). However, such changes are small and appear only in some of the fibers. In the intact animal variability of baroreceptor discharges due to physiological oscillations in pulse pressure makes it difficult to evaluate precisely the importance of this effect.

In an attempt to clarify whether baroreceptor activity is affected by sympathetic stimulation, a preparation of the carotid sinus and aortic arch *in vitro* was

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used. The effects of stimulation of sympathetic fibers directed to the aortic arch in the intact animal were also examined. The results support the idea that sympathetic fibers can modify the mechanical characteristics of the sinus and aortic arch walls and thus vary the pattern of discharge of baroreceptor fibers.

Materials and Methods

Experiments were performed in 74 adult cats (1.6-3.2 kg) anesthetized with sodium pentobarbital (35 mg/kg, i.p.). The saphenous vein was cannulated for injection of supplementary doses of anesthetic or other drugs. The trachea was cannulated and the animal artificially ventilated with air.

Experiments in the «intact» animal

In 25 cats, the aortic nerve and the stellate ganglion and its branches were exposed and dissected under a binocular microscope within the thorax (4). The nerves were placed on bipolar stainless steel electrodes and covered with mineral oil (37° C). After identification of the aortic nerve, by recording rhythmic activity synchronous with arterial pressure pulsations, small strands were obtained from the peripheral cut end by further dissection. Blood pressure was recorded with a Sanborn transducer through a catheter introduced into the femoral artery. Body temperature was maintained at about 37° C by means of radiant heat.

Experiments *in vitro*

A. *Isolated aortic arch.* The heart and its vessels, the lungs, the stellate and intermediate ganglia and their branches were excised from the cat and placed in Locke's solution (NaCl 9.0; KCl 0.42; $CaCl_2$ 0.34; CO_3HNa 0.2, glucose 1.5 g/l) previously saturated with 95 % O_2, and

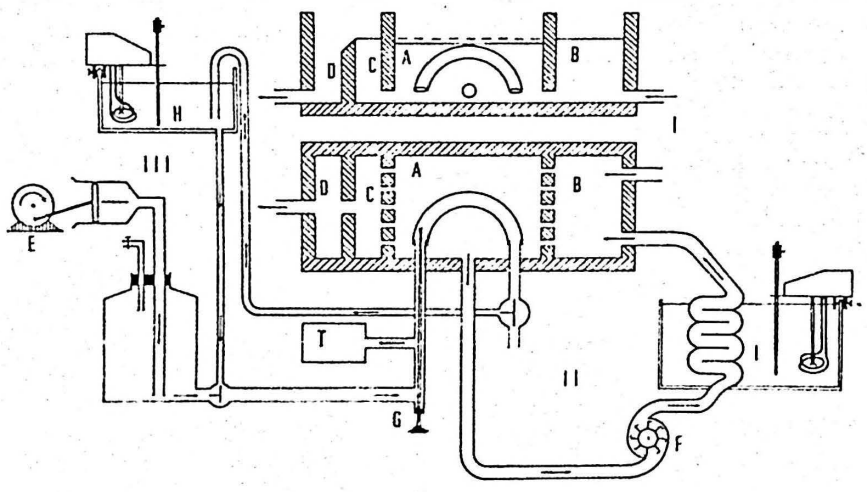

Fig. 1. *Schematic diagram of the set-up used for perfusion of carotic sinus and aortic arch.* I, experimental chamber with four compartments A, B, C, D, shown in both top and side view. A, contains artery in Locke's solution covered by paraffin oil where nerves are on recording and stimulating electrodes. B, communicates with A through many holes in the wall and contains Locke's solution bubbled with a mixture of 95 % O_2 and 5 % CO_2. II, perfusing system controlled by a roller pump (F). III, perfusing system controlled by a modified Dale-Schuster pump (E). In both systems the temperature was controlled by a stirred circulator (H, I). (T) transducer for measurement of pressure in the perfusion systems. (G) cannulae for infusion of drugs.

5 % CO_2 at 37° C; pH was adjusted to 7.43 by means of Tris-HCl buffer. The lungs, heart and pulmonary arteries were then removed. The aortic nerve was identified morphologically, the aorta was cleaned from surrounding tissues and all its branches tied. Accessory tissues were removed except those supporting the sympathetic ganglia and nerve branches. The preparation was then mounted in a plastic chamber (fig. 1) and superfused with flowing Locke's solution (150 ml/min). Two cannulae were then placed at both ends of the aorta and the artery was perfused internally with warm Locke's solution. Perfusion pressure was controlled with a modified Dale Schuster pump and adjusted with a resistance in the output tube. Rectangular or sinusoidal variations in pressure could be obtained by properly adjusting the output of the perfusion pump. Perfusion pressure was measured with a Sanborn transducer connected through a T-tube placed at the input of the artery.

B. *Isolated carotid sinus.* The carotid area was exposed and the carotid nerve, cervical superior and nodose ganglia were dissected free. The external carotid lingual, occipital and pharyngeal arteries were tied. The carotid artery including the carotid sinus area and its nervous connections (carotid nerve and vago-sympathetic trunk and ganglia) were excised and placed in the oxygenated warm Locke's solution. Once cleaned, the preparation was mounted in the same chamber used for the aortic perfusion and similarly superfused or perfused under pressure. Pressure was recorded through a T-tube at the input in the common carotid artery.

Recording and stimulation

Both in the experiments *in vitro* and in the intact animal, a thin filament (containing a single active baroreceptor unit) was obtained from the peripheral cut end of the sinus or aortic nerve and placed on bipolar stainless steel recording electrodes. For stimulation bipolar stainless steel electrodes were placed on sympathetic or on the aortic or carotid nerves. Rectangular pulse stimuli (0.5-2.5 msec) were delivered through a stimulus isolation unit (Grass SIU 5) driven by a stimulator which gave single or repetitive pulses (2-20/sec). Amplitude was adjusted in each case to be supramaximal for activation of sympathetic fibers in the stimulated nerve.

The stimulating pulses, the action potentials, arterial pressure and EKG in the experiments with the intact animal were displayed on separate channels of an oscilloscope (Tektronix 565) and stored on a magnetic tape recorder. For the *in vitro* experiments, the action potentials, stimulating pulses and perfusion pressure were recorded and stored on tape. The tapes were later analyzed with a Physioscope Intertechnique (DIDAC 800) from which number of impulses/beat and latency histograms of the first, second, and third impulse of the discharge measured from the R wave of the EKG were obtained. Arterial pressure was digitized and heart rate was obtained by measuring the intervals between the R waves of the EKG.

Results

A. Experiments in the intact animal

Succesful recordings were performed in filaments obtained from the aortic nerve in the thorax containing a total of 70 single baroreceptor units. Stimulating electrodes were placed on the preganglionic trunk of the stellate ganglion (to study 10 sensory units) or its postganglionic branches (ansa subclavia cranialis or caudalis) to study 60 sensory units. Intensity values twice that necessary to evoke a maximal response of sympathetic fibers in the aortic nerve were used during periods of 100-150 sec at frequencies of 3-15/sec. An increase in the heart rate and of the

systolic arterial pressure to 30-35 % above control values was obtained in all instances after 8-14 beats from the start of the stimulation. The number of baroreceptor impulses per beat also augmented. During stimulation the increase in pressure, heart rate and number of impulses per beat was gradual and maximal values (4-6 impulses per beat more than during control period) were obtained at its end. Interruption of the stimulus was accompanied by a sharp decrease in heart rate and number of impulses per beat which reached their control values within 15-20 sec.

The effect of a beta-blocking agent (propanolol hydrochloride 20 mg/kg, i.v.) was studied in 5 experiments in which a single baroreceptor unit was recorded. The heart rate, arterial pressure and number of baroreceptor impulses per beat fell shortly after the injection. Stimulation of the postganglionic sympathetic branches 15 min lated produced a slight increase in systemic arterial pressure and no clear changes in heart rate of number of impulses per beat. The alpha-blocking agent, tolazoline (2 mg/kg, i.v.) was administered in 3 different experiments; arterial pressure, heart rate and number of impulses per beat still increased during sympathetic stimulation 15 min after the injection, although the latency of the effect increased markedly and the magnitude of the change was reduced. Guanethidine (10 mg/kg, i.v.) injected in 5 animals completely blocked the effect of simpathetic stimulation 30 minutes after its administration.

In an effort to confine stimulation to sympathetic fibers directed to the aortic baroreceptor areas, a filament split from the peripheral cut end of the aortic nerve in the thorax was recorded from, while stimulation was applied to the remaining cut end of the nerve with trains of pulses synchronized with the R wave of the EKG (3-6 pulses separated by 5-10 msec). Lack of antidromic inhibition due to stimulus spread to the recorded fibers was confirmed by the absence of an antidromic pause when the stimulus was placed in the middle of the orthodromic bursts (3). In 8 animals in which this procedure was tried, stimulation of the aortic nerve produced either small increases or decreases in arterial pressure which were followed by slight changes in baroreceptor activity. In 4 preparations the number of impulses per beat during the stimulation period seemed to be reduced when compared with the same values of systolic pressure in the control period, however such comparisons were subject to error because the changes were of such small magnitude and no further experiments were performed.

B. Experiments *in vitro*

Carotid sinus baroreceptor in vitro In 15 preparations using the isolated carotid artery, the preganglionic sympathetic trunk was stimulated electrically with trains of pulses (amplitude 10 to 20 V; duration 0.5 to 2.5 msec; rate 10 to 10 pulses/sec) during periods of 60 to 90 sec.

In 10 experiments, step changes of perfusion pressure of 40 and 60 mm Hg were applied to the carotid sinus. Then at each static pressure level, a 0.8 hz sinusoidal oscillation with a peak-to-peak amplitude of 60, 80 and 90 mm Hg pressure were superimposed in each preparation. The maximal pressure used in these tests was 150 mm Hg.

A decrease in the number of impulses per oscillation of pressure was observed during sympathetic stimulation in 5 preparations. Such decrease varied between 18 % and 50 % of the control frequency and began to appear 10 to 16 sec after the onset of the stimulus. They persisted up to 10 sec after stimulation was interrupted. Significant increase in the time of appearance of impulses in each burst, in relation with the control period ($P < 0.001$) was observed during stimulation of the sympathetic nerves. In another preparation, sympathetic stimulation induced

an increase of 17 % in the number of impulses per oscillation but only when the maximal values of the sinusoidal pressure wave (60 to 150 mm Hg) was used. In the other four experiments no changes in the frequency of impulses could be observed during preganglionic stimulation of the sympathetic trunk. In the remaining 5 experiments the peak-to-peak amplitude in each preparation was kept constant (30 or 40 mm Hg) superimposed over a static pressure level of 80 or 100 mm Hg) while the frequency was varied, values of 0.3, 0.6, 1, 2 and 3 hz were chosen for this kind of experiment.

In four of the five mentioned above experiments a decrease in the number of impulses per oscillation (fig. 2A) and an increase in the time of appearance of the first 10 spikes was obtained during stimulation of the cervical sympathetic trunk with sinusoidal pressure in the range of 0.3 to 1 c.p.s. When variations at 2 and 3 c.p.s. were applied in the same preparation no changes were obtained. In the fifth experiment, impulse frequency remained unaltered for all the range of frequency oscillation explored.

In 13 different experiments, the carotid nerve was stimulated while afferent activity was recorded from a filament split from it. Steps changes of perfusion pressure ranging from 0 to 60 mm Hg were applied to the carotid sinus. Then at each static pressure level, a 0.5 hz sinusoidal oscillation with a peak-to-peak amplitude of 30, 50 and 60 mm Hg was superimposed. In 4 of these units, stimulation of the carotid nerve was performed using trains of pulses (amplitude, 2 or 3 V, duration 0.5 msec, frequency 15 or 20 pulses/sec) a sustained reduction in the number of impulses to 20 % to 30 % of the control appeared 6 to 8 sec after the onset of the stimulation. The initial values were obtained again shortly (6 to 10 sec after the interruption of the stimulus) (fig. 2). These preparations, as well as other 9 in which continuous trains of pulses were not employed, did not show changes in impulse frequency when 1 to 6 pulses separated by 50 msec were applied before the rhythmic discharge of spikes, by synchronizing the stimulator with the rising phase of the pressure wave.

In 6 of the experiments described above,

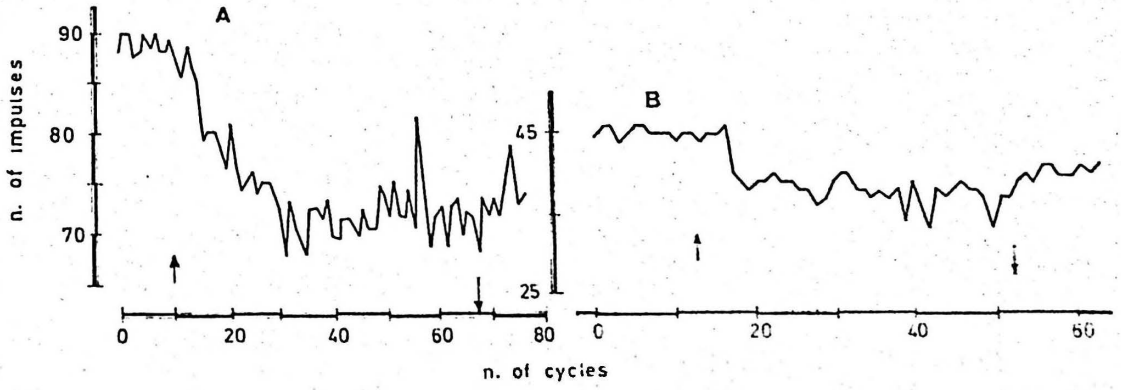

Fig. 2. *Changes in carotid nerve impulses per cycle of pressure in a carotid preparation in vitro.*

(A) preganglionic stimulation of sympathetic trunk. (B) carotid nerve efferent stimulation and recording in a filament of the same nerve. Parameters of stimulation: A, amplitude, 15V; duration, 2 msec and rate 15 pulses/sec. B, amplitude, 3V; duration, 0.5 msec and rate 20 pulses/sec. Perfusion with a sinusoidal wave of maximal pressure 120 mm Hg and minimal pressure 80 mm Hg. The frequencies of the sinusoidal wave were: A, 0.3 hz; B, 0.8 hz. Arrows indicate on and off stimulation.

Table I. *Effects of efferent stimulation of carotid nerve* in vitro.
Responses of carotid nerve baroreceptors to afferent stimulation of this nerve. Mean value and standard duration were calculated from 6 values.

Unit	Stimulus pulse duration (0.5 msec)	P.P. *	Number of Impulses Control	Stimulus	P **
71/94	(2 V; 15/sec)	70	23.66±3.05	14.25±3.86	0.05
71/94	(3 V; 15/sec)	60	18.25±0.50	13.50±1.73	0.005
72/1	(3 V; 20/sec)	60	16.62±3.54	9.44±1.81	n.s.
72/3	(3 V; 15/sec)	60	18.16±0.96	12.20±3.19	0.01
72/3	(4 V; 15/sec)	60	19.00±1.00	5.25±9.21	n.s.
72/29	(2 V; 20/sec)	70	28.50±0.57	24.75±2.75	0.05
72/34	(2 V; 15/sec)	70	26.50±1.73	21.66±3.21	0.05

* Perfusion pressure, mm Hg. ** Significance of differences relative to controls (t test). n.s. not significant.

abrupt increases (60 or 70 mm Hg) in the perfusion pressure of 4 sec duration were made. The fiber fired phasically during 0.5 to 1 sec when pressure increases of this amplitude were applied. The number of impulses during 5 to 8 of these variations made successively one after the other with an interval of 12 sec was measured. The numbers of impulses were compared during this procedure alone and when combined with simultaneous stimulation of the main trunk of the carotid nerve with a train of pulses (amplitude 2 or 4 V, duration 0.5 msec, frequency 10 or 20 pulses/sec). A reduction in the number of impulses was obtained in all instances during the stimulation period as shown in table I.

Aortic baroreceptors in vitro. A total of 13 preparations of the isolated and perfused aorta were made. In 9 experiments the effect of the postganglionic sympathetic stimulation (ansa subclavia cranialis or caudalis) on baroreceptor discharges was studied. Control discharges were obtained with intra aortic pulsatile pressures of 0.5 hz at 60 and 90 mm Hg of peak-to-peak amplitude superimposed over static pressures ranging from 20 to 50 mm Hg. The number of impulses per oscillation elicited by these pressure waves varied between 20 to 30 impulses. Control discharges were reduced by 2 or 4 impulses per oscillation of pressure wave, 8 to 16 sec after the beginning of the stimulation of sympathetic fibers in five prepa-

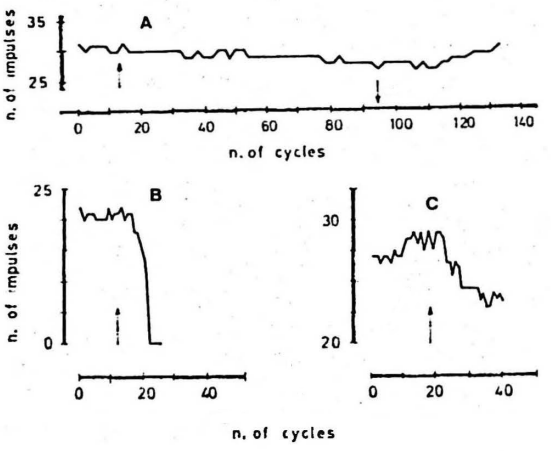

Fig. 3. *Change in a aortic nerve impulses per cycle of pressure.*
A, stimulation of a postganglionic branch of the stellate ganglion (ansa subclaviae cranialis) with 10V amplitude. 1.5 msec of duration and a rate of 10 pulses/sec during sinusoidal perfusion of aortic arch *in vitro* with a maximal pressure of 110 mm Hg and a minimal pressure of 90 mm Hg. The frequency was 0.8 hz. B and C, show the effects of addition of norepinephrine to the same preparation (6 μg/ml). In B maximal pressure of the sinusoidal wave was 140 mm Hg and the minimal pressure was 60 mm Hg. In C the maximal and minimal perfusion pressures were: 160 mm Hg and 80 mm Hg respectively. In both the frequency was 0.5 hz.

ration. The reduction of frequency persisted more than 20 sec, after stimulation was interrupted (fig. 3A). In the 4 remaining experiments no changes were elicited during the sympathetic stimulation.

In another 4 preparations, rectangular pressure variations from 0 to 90 mm Hg lasting 4-6 min were applied. When a steady state discharge was obtained, stimulation of the postganglionic branches of the stellate ganglion (amplitude 10 V; duration 2 msec; frequency 15 pulses/sec) was performed for 80 sec and the discharge frequency compared with those of the previous and subsequent periods. No changes in frequency were obtained during the stimulation periods.

Effects of norepinephrine. In 4 isolated preparations of the aortic arch and 3 of the carotid sinus, sinusoidal pressure waves (peak-to-peak amplitude ranging from 20 to 85 mm Hg superimposed over static pressures ranging from 20 to 60 and frequency 0.5 hz) were applied, and the number of impulses per cycle measured. With norepinephrine at a final concentration in the perfused Locke's solution of 5 to 10 μg/ml a reduction in the number of impulses per cycle was obtained, 10 to 15 sec after the beginning of the perfusion (fig. 3B, C). The reduction of frequency was smaller for higher amplitudes of the pulsatile pressure (fig. 3B, C). The effect of norepinephrine persited for 10 min after the perfusion with the solution containing the drug was interrupted and continued with fresh Locke solution.

Discussion

In the intact animal, sympathetic stimulation consistently produced arterial pressure elevations mediated by sympathetic fibers directed to the heart. The increases in aortic baroreceptor activity secondary to these arterial pressure changes masked any direct effect of sympathetic fibers on the aortic baroreceptors. Changes in arterial pressure of smaller amplitude were also observed during stimulation of the peripheral end of the aortic nerve, suggesting that at least part of the sympathetic fibers that enter this nerve (4) are directed to the heart. α and β-blocking agents failed to establish whether increases in baroreceptor activity elicited by sympathetic stimulation were solely due to changes in arterial pressure. Arterial pressure and heart rate changes disappeared after administration of propranolol, as well as the increase in impulse frequency, but the possibility that a direct effect of sympathetic fibers on baroreceptor activity was also blocked by the drug cannot be excluded.

In the isolated and perfused preparation, undesired variations of arterial pressure are absent; furthermore, the applied conditions, sympathetic stimulation produced a decrease, no changes or an increase in baroreceptor activity depending on the characteristics of the perfusion pressure (amplitude, mean pressure and frequency of the pressure oscillation) applied to the carotid artery or aorta. Nevertheless, a decrease in the frequency of baroreceptor impulses was observed in most preparations with the perfusion pressure values employed. More marked reductions in the frequency of impulses were obtained when norepinephrine was added to the perfusion fluid.

The dependence of these effects on the sinusal pressure, the latency of the frequency changes induced by the sympathetic and its persistence after interruption of the stimulus suggest that sympathetic effects on baroreceptor activity are exerted through mechanical changes occurring within the sinus wall secondary to the activation of its smooth muscle fibers. The quantitative differences between the response to electrical stimulation and to the application of norepinephrine might be due to the fact only a small fraction of

the smooth muscle fibers of the arterial stimulation (6) in contrast to the general activation produced by high doses of norepinephrine (7) as those used in the present experiments.

Evidence suggesting an inhibitory effect of sympathetic fibers on baroreceptor activity has been obtained in several studies; LANDGREN (13) observed a decrease in the frequency of impulses of baroreceptor fibers discharging high-amplitude spikes, when norepinephrine was applied to the carotid sinus area and the intrasinusal pressure was below 100 mm Hg; small amplitude spikes, however, increased their discharge frequency after application of the drug. Similar results were obtained by AARS (1) from aortic baroreceptor fibers when norepinephrine was infused intravenously in the rabbit and the diastolic pressure was kept between 40 and 80 mm Hg. More recently, KEITH *et al.* (10) found a reduction in baroreceptor activity originated in the right subclavian-brachiocephalic artery of the dog by the stimulation of its sympathetic supply.

In contrast to these results, a decrease in blood pressure suggestive of an augmented baroreceptor activity was obtained by local application of catecholamines on the carotid sinus wall (8) or by sympathetic stimulation (11, 16, 18). Reflex decreases of arterial pressure resulting from sympathetic stimulation or from local application of catecholamines on the sinus area are not a convincing evidence of an inhibitory effect of the sympathetic on the baroreceptor activity. They are presumably the result of the activation of the whole population of baroreceptor fibers and may merely indicate that the small-spike fibers have more potent reflex effects than high-amplitude spike fibers. Moreover, such reflex effects may be greatly modified by the procedure used to anesthetize the animal.

An increase in baroreceptor activity recorded from the carotid nerve under sympathetic stimulation was observed by KOIZUMI and SATO (12) in the opposum; SAMPSON and MILLS (19) also described in the cat a small increase in carotid baroreceptor activity during sympathetic stimulation, which persisted after the systemic arterial pressure increases induced by such stimulation were prevented by cutting all cervical sympathetic branches except those directed to the sinus area.

The discrepancies between the data obtained in the intact animal and in the isolated preparation when baroreceptor activity is measured while the sympathetic is stimulated may be partially explained by the different experimental conditions in both types of experiments. In the *in vitro* preparation the artery was perfused with an artificial solution at a flow rate different from that found in the intact animal; the mechanical conditions of the arterial wall (longitudinal and radial elastic tensions) were changed; the shape of the pressure oscillation was different and the pressure values employed *in vitro* were below 110 mm Hg in most experiments.

It is also conceivable that the different results obtained *in vivo* by SAMPSON and MILLS (19) compared with those observed in the isolated preparation are the consequence of a different behaviour of fibers displaying high-amplitude spike according to the different values of intrasinusal pressure and the mechanical conditions of the sinus wall. Such differences may be due to variations in the location of the nerve endings in relation to the arterial wall components, making the endings with large spikes more sensitive to the distensibility properties of the sinus wall; this could explain the decrease discharge frequency that appears at low intrasinusal pressure values, at which the effective distensibility of the sinus wall seems to be reduced (2, 13). It is an open question whether the observed decreases in baroreceptor activity during sympathetic stimulation at low pressures in the isolated carotid sinus have a significance in the reflex control of arterial pressure.

Resumen

Se estudian en el gato intacto y durante la perfusión *in vitro* del arco aórtico los efectos de la estimulación del ganglio estrellado sobre la descarga de fibras barorreceptoras contenidas en el nervio aórtico izquierdo. Asimismo, han sido estudiados los efectos de la estimulación del tronco simpático cervical sobre la descarga barorreceptora del nervio carotídeo durante perfusión *in vitro* del seno carotídeo. En el animal intacto, la estimulación del ganglio estrellado o del nervio aórtico produce un simultáneo incremento en la presión arterial, frecuencia cardíaca y número de impulsos registrados en un filamento del nervio aórtico izquierdo. En los estudios de perfusión *in vitro* aparece en la mayoría de los casos una disminución en el número de impulsos barorreceptores tanto en el nervio carotídeo o aórtico durante la estimulación del simpático. Estos efectos eran únicamente observados cuando ambos valores de la presión y frecuencia de las ondas de perfusión eran bajos. La infusión de noradrenalina producía una disminuación más marcada.

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