Central neural regulation of carotid baroreceptor reflexes in the cat

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REIS, DONALD J., AND MICHEL CUENOD. Central neural regulation of carotid baroreceptor reflexes in the cat. Am. J. Physiol. 209(6): 1967–1979. 1965.—Reflex changes of the mean aortic blood pressure (BP) to carotid sinus stretch or carotid occlusion in anesthetized vagotomized cats were observed following ablation or electrical stimulation of brain. Decerebration produced augmentation of the depressor response to sinus stretch, reduction of the pressor response to carotid occlusion, and fall of BP. Subsequent cerebellectomy produced an increase of depressor and pressor responses. Midpontine section produced disappearance of the pressor response to carotid occlusion and appearance of a “paradoxical” pressor response to sinus stretch. Stimulation within hypothalamus and reticular formation produced augmentation and a barbiturate-sensitive post-stimulus depression of pressor response without changes in BP. It is concluded that baroreceptor reflex responsiveness is under tonic and phasic control of brain structures above medulla and that pressor and depressor limbs of the reflex are not reciprocally modified independently of each other and of the BP. This suggests functional separation of brainstem neurons involved in reflex and tonic BP control and that some cerebral regulation of BP is indirectly mediated through vascular reflexes.

CNS and baroreceptor reflex; vagotomized cats; decerebration; cerebellectomy; pontine section; electrical stimulation: hypothalamus; reticular formation; depressor reflex; pressor reflex; arterial pressure; carotid occlusion

In the following study we have investigated the role of the brain lying above the medulla in modifying baroreceptor reflex responsiveness. The possibility of supramedullary control of the reflex has been suggested by the observations that carotid sinus responsiveness changes during the elevation of blood pressure accompanying feeding behavior in the dog (2) or electrical stimulation of the hypothalamus in the cat (17). The hypothesis is supported by the anatonical evidence of cerebral projections to the nucleus of the tractus solitarius (4), the probable site of termination of baroreceptor afferent fibers (9, 20).

It is not known if baroreceptor reflex responsiveness may be altered independently of changes in the systemic blood pressure. Hence, it has not been established whether cerebral regulation of the reflex mechanisms may be distinct from any cerebral influence on the neurons of the lower medulla and pons, the brainstem vasomotor neurons, which are necessary for maintaining normal levels of blood pressure (1, 3). To our knowledge, only one previous study has suggested that the reflex may be changed by the brain independently of the blood pressure. Moruzzi (26) in the vagotomized cat demonstrated that the rise of blood pressure elicited by prolonged carotid occlusion and the fall elicited by electrical stimulation of the depressor nerve were both inhibited by an electrical stimulus simultaneously delivered to the anterior cerebellum, which, by itself, did not change the blood pressure. Although it is not certain that the blood pressure responses tested were exclusively baroreceptor, Moruzzi’s study suggests a functional distinction between brainstem mechanisms maintaining blood pressure levels and those regulating vascular reflex excitability.

In this investigation we have sought to determine, by ablating or electrically stimulating the rostral brain areas, if the blood pressure responses of the baroreceptor reflex may be modified independently of the systemic blood pressure in cats with both vagi and one carotid sinus nerve sectioned. Both the pressor response to carotid occlusion and the depressor response to carotid sinus stretch have been tested in order to sample each end of the baroreceptor stimulus/response curve (21) and to see if both extremes of this curve change in any constant relationship to each other. The extremes were tested because of the reproducibility of the stimulus. Preliminary reports of these findings have been made (28, 29).
TABLE 1. Mean blood pressure and magnitude of depressor response to carotid sinus stretch and pressor response to carotid occlusion before and after decerebration

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Anesth.*</th>
<th>Before Decerebration</th>
<th>After Decerebration</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>BP, mm Hg ± 1 SD</td>
<td>SS, mm Hg ± 1 SD</td>
</tr>
<tr>
<td>1</td>
<td>N</td>
<td>132 ± 4</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>199 ± 18</td>
<td>43 ± 4</td>
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<tr>
<td>5</td>
<td>N</td>
<td>170 ± 6</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>13</td>
<td>C+P</td>
<td>150 ± 7</td>
<td>19 ± 3</td>
</tr>
<tr>
<td>30</td>
<td>C+P</td>
<td>96 ± 2</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>31</td>
<td>N</td>
<td>99 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>32</td>
<td>C</td>
<td>134 ± 15</td>
<td>48 ± 3</td>
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<td>34</td>
<td>C+P</td>
<td>133 ± 11</td>
<td>50 ± 2</td>
</tr>
<tr>
<td>35</td>
<td>C+P</td>
<td>199 ± 3</td>
<td>45 ± 3</td>
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<tr>
<td>36</td>
<td>C+P</td>
<td>113 ± 2</td>
<td>29 ± 3</td>
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<tr>
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<td>C+P</td>
<td>106 ± 7</td>
<td>61 ± 4</td>
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<tr>
<td>40</td>
<td>C+P</td>
<td>118 ± 6</td>
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</tr>
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<td>47</td>
<td>C+P</td>
<td>141 ± 6</td>
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<td>61 ± 3</td>
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<tr>
<td>Mean</td>
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<td>138 ± 6</td>
<td>25 ± 7</td>
</tr>
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</table>

BP = blood pressure; SS = sinus stretch; C.O. = carotid occlusion.
*Anesthetics: C = chloralose; N = pentobarbital sodium (Nembutal); P = thiopental sodium (Pentothal); E = ether.

METHODS

Preparation

Thirty-seven were anesthetized with 1% alpha-chloralose (60 mg/kg) often augmented during induction with a small intravenous dose of sodium thiopental (Pentothal) (5 mg/kg) to reduce collateral lcers. Six animals were anesthetized with sodium pentobarbital (Nembutal, 40 mg/kg intraperitoneally) and five were decerebrated while under ether anesthesia. The right carotid sinus area was used for testing. The right occipital and internal carotid arteries and the cannulated external carotid were ligated to reduce collateral flow back into the sinus during common carotid compression (8). The opposite carotid sinus nerve and both cervical vagi as well as both hypoglossal nerves were severed.

Recording

Aortic blood pressure was measured through a femoral catheter connected to a Statham pressure transducer (model 23 Db), heart rate was integrated by a Grass cardiotachometer triggered by the aortic pulse wave. Respiration was recorded from a tracheal cannula through a Statham pressure transducer attached to a modified Donald Christie apparatus (7). The pressure in the innervated carotid sinus was recorded through a cannula inserted through the proximal end of the ligated external carotid artery. It was connected to a Statham transducer through a three-way stopcock which permitted recording of endosinus pressure during introduc-

tion of fluid for baroreceptor stimulation. All transducers were led through modulator-demodulator units to channels of a Grass model 111-1 polygraph.

Baroreceptor Stimulation

Carotid baroreceptor reflex activity was elicited either by occluding the common carotid artery below the innervated sinus or by stretching the carotid sinus. The carotid artery was occluded almost instantaneously by compression with the head of an ordinary camera cable attached to a small Lucite block which was grooved to hold the carotid artery and rigidly sutured to the deep cervical muscles. Occlusion was sustained for 15-20 sec, the minimal time which predictably produced a maximal pressor response. With major collaterals to the sinus ligated, this maneuver results in a fall of intrasinus pressure below threshold for most baroreceptors (22).

The carotid sinus was stretched by the introduction of 2-3 ml of warmed heparinized saline pulse by the plunger of a syringe at the frequency of the cat's heart rate (35) for 5-10 sec and at a pressure greater than 290 mm Hg, which is excess of the pressure required to maximally stimulate baroreceptor afferents (22). The common carotid artery was simultaneously occluded proximally in order to prevent runoff of fluid. This maneuver produced a maximal depressor response. In some experiments, exclusion of chemoreceptors was accomplished by introduction of several 0.1-ml doses of 1% acetic acid into the sinus area (12).

In four animals an isolated carotid sinus was prepared by the Moisjecf technic (ref. 16, p. 30). Warm oxygenated saline was introduced at different static pressures from an oxygen tank by the method of Landgren (22) and stimulus/response curves (21) plotted.

Truncation

The brainstem was sectioned above the tentorium after ligation of the other external carotid artery. Section was performed under direct vision by making a partial incision with a spatula and then completing the separation by suction. Cerebellectomy was performed by suction alone. The exposed floor of the fourth ventricle was protected by a pool of warm mineral oil. Section of the brainstem below the tentorium was always done by spatula under direct vision through a dissecting microscope. In one animal, pontomedullary lesions were made by a ventral approach through the roof of the mouth.

Electrical Stimulation

The electrodes, described elsewhere (25), were made of Teflon-coated 0.006-inch stainless steel wire lying within 28-gauge stainless steel tubing with a 0.5-mm bared tip. Monopolar stimulation was used. The electrodes, placed stereotactically, were cathodal to a needle electrode inserted in the posterior cervical muscles. The stimulus was generated by Tektronik waveform (no. 162) and pulse generators (no. 161) and led through a Grass...
TABLE 2. Mean blood pressure and magnitude of depressor response to carotid sinus stretch and pressor response to carotid occlusion in decerebrate cats before and after cerebellectomy

<table>
<thead>
<tr>
<th>Cat No</th>
<th>Anesth.</th>
<th>Decerebration Alone</th>
<th>Decerebration Followed by Cerebellectomy</th>
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<tr>
<td></td>
<td></td>
<td>BP, mm Hg ± SD</td>
<td>SS, mm Hg ± SD</td>
</tr>
<tr>
<td>31</td>
<td>N</td>
<td>81 ± 5</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>36</td>
<td>C + P</td>
<td>81 ± 5</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>38</td>
<td>C + P</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>39</td>
<td>C + P</td>
<td>72</td>
<td>9</td>
</tr>
<tr>
<td>40</td>
<td>C + P</td>
<td>81 ± 3</td>
<td>23</td>
</tr>
<tr>
<td>47</td>
<td>C + P</td>
<td>117 ± 15</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>49</td>
<td>E</td>
<td>142 ± 2</td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td>90 ± 4</td>
<td>13 ± 6</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

RF isolation unit. Stimulus current was monitored as described by MacLean and Ploog (25). Frequencies of 5, 30, and 100 cycles/sec with pulse durations of 2.0, 1.0, and 0.1 msec, respectively, were applied for 20 sec. Stimulus intensity ranged from 0.2 to 1.0 ma in most experiments.

Histologic Examination

The animals were sacrificed by perfusion through the heart with normal saline followed by 10% Formalin. After fixation, the brains were sectioned, frozen, or embedded in celloidin. Facing sections were stained with cresyl violet for cells and Lillie's variant of the Weil method for fibers. The location of electrodes or the plane of truncation was then reconstructed. The detailed histologic methods have been described elsewhere (25). At the end of each experiment, the innervated carotid sinus area was inspected for clots. Since these may alter the reflex response, animals with clots were discarded from this study.

General Procedure

After the completion of the preparation and when the blood pressure had stabilized, a series of control values, usually four or eight trials, for pressor and depressor responses were obtained. Following this, attempts were made to alter the reflex responses by truncation or electrical stimulation. After truncation, at least 30 min were allowed to elapse before the reflexes were again tested. With electrical stimulation of the brainstem, the usual procedure was to obtain a control series of reflex responses, observe the effect of stimulation on the baseline value of blood pressure, and then note the effects of combined stimulation of brainstem and baroreceptors.

Analysis of Results

The reflex changes in aortic blood pressure were calculated as changes in the mean blood pressure (the diastolic pressure plus one-third of the pulse pressure). The absolute blood pressure response to carotid occlusion or sinus stretch after neural intervention was compared with the control responses. Changes were expressed as percentages of the control. When applicable, statistical analysis was done.

RESULTS

Control Responses

Stretching the carotid sinus with intraluminal pressure of 230 mm Hg or more produced a fall in mean aortic pressure averaging 26 mm Hg (range: 6-51 mm Hg) (Table 1). This was the maximal depressor response. With rapid pulsing stimulation, the blood pressure reached the nadir within 5-10 sec and returned to base line 10-15 sec after the stimulus ended. The magnitude of the response varied little within a testing period. Changes in heart rate with sinus stretch were inconsistent, independent of the depressor response, and when present consisted of a slight bradycardia. Reduction in the depth and frequency of respirations, or even apnea, was almost invariably associated with sinus stimulation. Usually respiratory changes lasted for only one breath preceding the fall of blood pressure (see Fig 1) and probably did not contribute to the magnitude of the depressor response, since on repeated trials no relationship between the magnitude of the respiratory and of the vasomotor responses was demonstrated.

Complete occlusion of the common carotid artery resulted in a prompt rise in the aortic blood pressure averaging 40 mm Hg (range: 13-73 mm Hg). It reached its maximum within 10-20 sec. Changes in heart rate were inconsistent, but when present consisted of slight acceleration. An increase in the depth and rate of respiration occurring 10 sec after the onset of the stimulus was seen once in an unanesthetized, decerebrated animal. Introduction of several 0.1-ml doses of 1% acetic acid into the sinus area to destroy the chemoreceptors (12) resulted in the gradual diminution and final disappearance of the respiratory component without any change in the blood pressure response. Both depressor and pressor responses disappeared with section of the remaining carotid sinus nerve, indicating the reflex nature of the responses.

Truncation

Serial transections of the brain were performed successfully in 18 animals. Three principal lesions were made: 1) decerebration, 2) cerebellectomy, and 3) pontine section. In addition, the effects of transections at the cervicomedullary junction were observed. Although various combinations of lesions were made in different animals and in some experiments only sinus stretch or carotid occlusion was tested, the patterns of change of blood pressure, heart rate, and the reflex response to carotid sinus stimulation were qualitatively
FIG. 1. Effect of decerebration, cerebellectomy, and pontine transection on reflex changes in heart rate (HR), aortic blood pressure (BP), and respiration following carotid occlusion (C.O.) and supramaximal sinus stretch (SS) in a representative experiment. Cat, chloralose anesthesia, bilateral vagotomy, section of left carotid sinus nerve. Note in "control" rise of BP, and acceleration of HR during C.O. and drop of BP, slowing of HR and hypoapnea with SS. At 1, after midcollicular decerebration reduced consistent from animal to animal for lesions placed at similar levels of the brain.

The data from these experiments are presented in Tables 1 and 2. Where applicable, the standard deviation has been provided, but on a few occasions technical problems limited the number of measurements. A representative experiment in which characteristic changes in cardiovascular function resulted from lesions made at the three principal levels is illustrated in Fig. 1. The following summarizes our observations:

1) Decerebration. The term "decerebration" is used in this study to denote any section of the brainstem between the collicular plate dorsally and the base of the brain up to the optic chiasm rostrally and the pontomesencephalic border caudally. It was performed in 15 animals after base lines had been established (Table 1). In one animal the rostral section was between a point just ahead of the superior colliculus dorsally and the caudal edge of the optic chiasm ventrally. In three animals the section passed between the same dorsal landmark and a point just in front of the mammillary bodies. In the remainder, the sections were made in varying planes between the colliculi and the base of the midbrain as far back as the rostral border of the pons. The patterns of change in cardiovascular function resulting from truncations in this wide region were similar, although the degree of skeletal muscle rigidity varied. The changes observed were: a) A fall of the mean aortic blood pressure from an average control level of 138 mm Hg to an average of 101 mm Hg. For 12 of the 15 de-
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After cerebellectomy, in several animals, a marked "rebound" overshoot of the blood pressure followed on the reflex blood pressure drop to sinus stretch. An unusually large response is illustrated in Fig. 2. The opposite phenomenon, a rebound fall following the pressor response to carotid occlusion, was not seen.

2) Pontine and medullary sections. Serial transections of the brainstem below the midbrain were made in 13 animals. Of these, 12 were performed on cerebellectomized, decerebrated animals. In one, the lesion was placed by a ventral approach, leaving the cerebellum intact. Transections of the rostral pons resulted in apnea, as is usual in vagotomized animals with lesions at this level. The blood pressure and the heart rate underwent a marked initial increase following rostral pontine lesions in vagotomized animals (14). This elevation was not usually sustained, however, and after several minutes both heart rate and blood pressure tended to drift down to levels which were the same as or lower than those seen prior to section.

A critical level for baroreceptor responses was found at the level of the facial colliculus. In five animals, sections passing through this dorsal landmark and through the superior olivary complex between its middle and the rostral pole resulted in the following cardiovascular pattern (Fig. 1): a) little or no change in blood pressure or heart rate; b) a "paradoxical" rise of blood pressure with sinus stretch rather than the usual fall and sometimes associated with a slight bradycardia; c) the complete disappearance of the pressor response to carotid occlusion in four of the five animals. In the one animal in which the lesion was made through the ventral approach, the pressor responses persisted.

More caudal sections through the medulla at a level just ahead of the rostral pole of the inferior olive resulted in a further fall in blood pressure to a mean level of about 70 mm Hg and disappearance of responses to carotid sinus stretch or carotid occlusion. The appearance of a paradoxical pressor response to carotid stretch following transection of the lower pons suggests that the depressor response depends on the integrity of structures within this area. The absence of the depressor response in this instance cannot have been the result of the blood pressure having reached a minimum, since medullary section produced a further fall. This unmasking of a pressor response to stretch also poses the question as to whether or not there may be an unsuspected pressor component associated with baroreceptors.

Electrical Stimulation

Discrete areas of the brainstem were electrically stimulated to determine if the carotid baroreceptor reflex could be phasically altered by structures other than the cerebellum (26), and if the induced changes in reflex excitability could occur in a graded manner independent of any changes in cardiovascular function. Electrodes were placed in regions from which vasoconstrictor responses had been elicited by others (19, 31). Changes in the

cerebral animals this represented an average drop of 27%. For the other three animals the drop of blood pressure was less than 10%. b) A slowing of the heart rate from a mean of 156 to 128 beats/min. c) An augmentation of the reflex drop of pressure to sinus stretch. This reflex was tested in 9 of the 15 decerebrated animals. In eight, the depressor response increased from an average control fall of 26 mm Hg to an average of 34 mm Hg, and in one a slight decrease was seen. The average increase in the depressor response was 34% \((P = 0.001)\). d) A significant \((P = 0.002)\) diminution of the pressor response to carotid occlusion which was reduced from an average control response of 40 to 19 mm Hg. In one animal the response to carotid occlusion was augmented rather than depressed following decerebration. For the group, the average reduction was 53%.

In 5 of the 15 animals, the initial rostral decerebration was followed by a second caudal transection within the confines of the zone defined above. In no instance did this second section alter the pattern of cardiovascular changes resulting from the initial decerebrating transection.

The effect of these modifications of blood pressure and heart rate was examined in vagotomized animals (14). This elevation was not usually sustained, however, and after several minutes both heart rate and blood pressure tended to drift down to levels which were the same as or lower than those seen prior to section.

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magnitude of the vasomotor responses to carotid occlusion or sinus stretch during and following stimulation were observed as follows:

**Carotid occlusion.** When electrical stimulation was delivered to points from which changes in blood pressure could be elicited within the mesencephalic reticular formation, the central tegmental tract, the anterior hypothalamic nucleus, and zona incerta, changes in the reflex pressor response were usually seen. Both potentiation and depression of the response were observed as described below.

a) A potentiation of the pressor response to carotid occlusion was commonly observed (Figs. 4 and 5) to appear concurrently with the electrical stimulus. The potentiation of the response always occurred at stimulus intensities below threshold for any induced change in the control level of blood pressure and increased in a graded manner in response to graded increments in the stimulus intensity. A stimulus intensity curve, plotted as percentage increase over a control response for an unusually large potentiation noted in an animal in moderately deep anesthesia, is illustrated in Fig. 3. In this experiment, graded increases in the intensity of the stimulus over a narrow current range resulted in almost a sixfold increase of the pressor reflex before any change was observed in the base-line blood pressure. Although in this particular experiment increasing the stimulus current resulted in a fall of blood pressure, potentiation of the pressor reflex also occurred at loci from which an increase in the stimulus strength resulted in a rise of base-line blood pressure.

b) Immediately following the electrical stimulus, there was a short period in which the pressor responses to carotid occlusion were reduced or even absent (Fig. 4). The intensity and duration of this poststimulatory reduction of pressor response were directly related to the intensity of the stimulus (Fig. 4, bottom). This inhibitory phenomenon could be selectively abolished transiently by small intravenous doses of Pentothal (3-5 mg/kg) which failed to affect the base-line blood pressure or the potentiation of the pressor response during electrical stimulation.

c) An especially prolonged inhibition of the pressor response to carotid occlusion followed brain stimulation in one experiment and is demonstrated in Fig. 5. Here, electrical stimulation in the posterior hypothalamus (Fig. 6) at 30 cycles/sec (Fig. 5, A) caused no change in the base-line blood pressure but did produce the usual potentiation and mild poststimulation depression (Fig. 5, B, 1 and 9). Immediately thereafter, another stimulus at 5 cycles/sec which itself produced only a slight fall of blood pressure (Fig. 5, C) was followed by a prolonged reduction of the pressor response which could be temporarily returned to control level when paired with stimulus at 30 cycles/sec (Fig. 5, D). The inhibition was abolished 12 min after its onset by intravenous Pentothal (Fig. 5, E) and could not immediately be re-established (Fig. 5, E, 16). This prolonged inhibition shows many of the characteristics of the brief poststimulus inhibition and probably is produced by similar mechanisms.

It is clear from these experiments that marked inhibitory and facilitative changes in the excitability of the pressor response to carotid occlusion can be elicited by electrical stimulation at many sites within the brainstem, and in the absence of any demonstrable change in the mean blood pressure. These changes may be graded and are completely reversible.

**Sinus stretch.** In contrast to the ease with which potentiation and depression of the pressor response to carotid occlusion were elicited, electrical stimulation never significantly changed the depressor response to sinus stretch. On occasion, a single stretch response would appear larger or smaller during electrical stimulation than the control, but these alterations were variable and inconsistent.

To test whether the stimulation would affect the threshold or contour of the baroreceptor stimulus/response curve rather than the size of the maximal drop, curves were obtained in four animals by introducing warm saline at different static pressures into a vascularly isolated innervated carotid sinus (15). Curves were plotted before and during electrical stimulation of points in the zona incerta and anterior hypothalamus. The stimulation intensities were adjusted so that the base-line blood pressure did not change before the endosinus pressure was increased. Electrical stimulation did not change these curves.

**DISCUSSION**

*Identity of the Vascular Reflex*

The reflex changes in blood pressure demonstrated in this study to be influenced by rostral brain areas are probably baroreceptor in origin. The depressor response is undoubtedly baroreceptor, since no other stretch-
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Fig. 4. Top: representative example of alterations in pressor response to repeated carotid occlusion (C.O.) (solid line above blood pressure record) during and after 30 sec of electrical stimulation of anterior hypothalamus. Note slight increase of pressor response during stimulation, absence of response 10 sec after stimulation, and gradual return over the next 3 min. Cat, chloralose anesthesia, bilateral vagotomy, and unilateral carotid sinus nerve section. Bottom: same animal as above. Relationship of intensity and duration of poststimulatory inhibition of pressor reflex to C.O. to intensity of electrical stimulation of anterior hypothalamus. Each line represents series of tests of C.O. following hypothalamic stimulation at different stimulus intensities.

Locus of Induced Alteration of Baroreceptor Responsiveness

It may be assumed that the changes in baroreceptor reflex responsiveness which followed destruction or stimulation of the brain resulted from change in excitability within the central pathways of the reflex arc for several reasons: a) since the reproducibility of the test stimuli was assured by the use of stimuli designed to test both the maxima and minima of the baroreceptor stimulus/response curve, the effects were not the result of fluctuation in the stimulus intensity; b) section of the vagi and opposite carotid sinus nerve eliminated possible variability of the response due to compensatory baroreceptor reflexes; c) vagotomy also excluded any constant contribution of heart rate to the magnitude of the blood pressure responses; after vagotomy, reflex changes in heart rate were negligible; d) since the effect of adrenomedullary catecholamines and vasopressin on baroreceptor reflexes is well known (16, 17) and none of our findings are explicable on an action of these agents on baroreceptors or blood vessels, it is unlikely that our results are due to their liberation as a result of cerebral stimulation or ablation.

Independence of Baroreceptor Reflex Responses and Blood Pressure

Cerebellectomy and electrical stimulation have demonstrated that the blood pressure response to baroreceptor stimulation may be modified by the brain without change in the systemic blood pressure. Similar alterations of vascular reflex responsiveness without associated
change in the systemic blood pressure resulting from modification of the cerebral outflow have been produced by Moruzzi (26), Gellhorn et al. (11), and Newman and Wolstencroft (27). Conversely, Wilson et al. (35) have shown that the blood pressure may be elevated by hypothalamic stimulation without changing the magnitude of the depressor response to carotid sinus stretch.

The absence of a change in the systemic blood pressure during brain stimulation or after ablation does not preclude wide shifts in local blood flow (10). By cancellation these changes may fail to be reflected in the systemic circulation. Hence, it is not permissible to draw conclusions about the peripheral cardiovascular mechanism from observations of the aortic pulse wave alone. However, the brainstem vasomotor neurons seem to integrate regional vascular activity by changing the sympathetic preganglionic output (24) in order to maintain a steady normal blood pressure in the systemic circulation (where the baroreceptors are located). Since the baroreceptor efferents appear to produce their effect on the blood pressure by modulating the tonic activity of these brainstem neurons, the observed capacity for independence of the blood pressure and the blood pressure suggests that there is some functional separation between the brainstem neurons participating in determining baroreceptor reflex responsiveness and those maintaining a normal blood pressure.

**Independence of Pressor and Depressor Mechanisms**

Another feature in this study is that the changes in the magnitude of the pressor and depressor responses following alteration of cerebral function were not similar nor were they reciprocal. This demonstration of the capacity for mutual independence of the responses representing the two extremes of the baroreceptor stimulus/response curve (21) is analogous to the observations of Glick and Braunwald (14) that the reflex vagal brady-
cardia and sympathetic tachycardia of baroreceptor origin in dog are not reciprocally linked. The present findings suggest, therefore, that the central neuronal mechanisms transducing an increase or decrease of baroreceptor afferent discharge into a fall or rise of blood pressure, respectively, are in part distinct from each other as well as from the mechanism maintaining the normal blood pressure.

Tonic Influences

The sustained changes in baroreceptor reflex responsiveness following decerebration and cerebellectomy indicate that both the pressor and depressor responses are under tonic control of structures rostral to the lower brainstem. Both telencephalon and cerebellum contribute to this tonic control, whereas transection at various levels revealed, in confirmation of Bronk et al. (5), that hypothalamus and midbrain are of little importance in this regard.

The net effect of the telencephalic outflow is to potentiate the pressor and reduce the depressor responses, since decerebration results in reduction of the former and in augmentation of the latter response. The demonstration that subsequent cerebellectomy restores the magnitude of the pressor response to or near control levels indicates that the reduction of this reflex in the decerebrate animal is the result of inhibition rather than destruction of neurons involved in the reflex itself.

The fall of blood pressure which followed decerebration poses the question as to whether the forebrain may not, in addition to its effect on the baroreceptor reflex, also contribute a tonic influence to the mechanisms maintaining normal blood pressure. We have demonstrated elsewhere (30) that the magnitude of this fall in our animals is only sufficient to cancel the rise of pressure produced by the initial section of the two vagi and one carotid sinus nerve, thereby bringing the blood pressure back to, but not below, the control level. Decerebration in animals with these nerves intact does not change the blood pressure, in confirmation of many others (3). These observations and the fact that cerebellectomy does not alter the base-line blood pressure (33) suggest that forebrain and cerebellum principally influence tonically only those brainstem mechanisms involved in the reflex blood pressure changes, rather than those necessary for maintaining the resting levels of the systemic pressure.

Phasic Influences

The baroreceptor reflexes may also be influenced phasically, as evidenced by the effects of electrical stimulation of hypothalamus and midbrain. Although it is not possible to discern by our techniques whether the changes resulted from excitation of fibers of passage or of intrinsic nuclear groups, it may be concluded that within these regions are structures capable of altering the reflex responses, and which do so at a lower threshold than required to alter the blood pressure.

In contrast to the effects of cerebellar stimulation (26), only the pressor response was modified by the brainstem stimulation. The failure to influence the depressor response is in accord with the observations of Wilson et al. (35) and at variance with those of Hilton (17). However, nuclei or pathways contributing to control of the depressor responses may have been missed in this limited exploration.

Some Functional Implications

This study indicates that the brain exerts some control over the excitability of the blood pressure responses of the baroreceptor reflex. That this suprasegmental control is exerted on a complex neuronal organization of the reflex seems likely in view of the multiplicity of ways in which these reflexes may be altered. The independence of the reflex responsiveness from the blood pressure, and the mutual independence of pressor and depressor responses suggest that the neurons subserving the reflex, as distinct from those maintaining the blood pressure, consist of at least two subdivisions: one responding to augmentation and the other to withdrawal of the baroreceptor barrage. Thus these neurons linked in the reflex chain act like interneurons being interposed between the baroreceptor afferent fibers and the brain.
stem vasomotor neurons whose activity they modify (24).

It is likely that these baroreceptor interneurons are in part the site of termination of the suprasegmental pathways which act on the baroreceptor mechanisms. In this manner it is understandable how, by influencing the reflex transmission, forebrain and cerebellum may exert a tonic influence on the baroreceptor reflex without providing much, if any, similar control of the resting blood pressure (3, 30). It also offers an explanation of why electrical stimulation of the upper brainstem affects the reflex responses at lower intensities than required to change the blood pressure. These observations suggest therefore that some measure of the cerebral regulation of blood pressure is exerted indirectly through modulation of the excitability of baroreceptor and possibly other vascular reflexes.

Whether or not there is anatomic separation between these proposed interneuronal populations and the brainstem vasomotor neurons cannot be postulated from our data. It is possible that all are admixed. If so, truncation would result in a parallel decline of the systemic blood pressure. It is possible that all are admixed. If so, truncation

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This proposal of a rudimentary model of the organization of the brainstem mechanism involved in tonic and reflex blood pressure control is supported by recent anatomic and physiologic evidence (9, 18) indicating the polyneuronal character of the baroreceptor reflex within the brainstem. Furthermore, microelectrode studies of neurons in the brainstem responding to baroreceptor input or changes in blood pressure (32, 34) have demonstrated several neuron populations whose behavior corresponds to that of the cells we proposed on theoretical grounds. Hence, our interpretation is compatible with present knowledge of brainstem cardiovascular mechanisms.

Nevertheless, by whatever means these modulations of baroreceptor reflexes are effected, it is clear that there is potentially great plasticity of the baroreceptor mechanisms. Although acute experimentation cannot answer how these mechanisms serve in life, they indicate that the brain has the capacity to selectively modify the reflex to protect either against a rise or against a fall in blood pressure. The brain, thereby, may reset the "barostat" in order to achieve some adaptive end for the organism.

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