Termination and secondary projections of carotid
sinus nerve in the cat brain stem

MITSUHIKO MIURA AND DONALD J. REIS
Department of Neurology, Cornell University Medical College, New York City 10021

THE CAROTID SINUS NERVE (CSN), a branch of the IXth
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activity evoked by electrical stimulation of the carotid sinus nerve
(CSN) were recorded with microelectrodes in the medulla and
poms of anesthetized, paralyzed cats. A short-latency (0.7-1.4
msec), monosynaptic, “early” response, triggered by myelinated
CSN fibers, was found in the intermediate portion of the nucleus
tractus solitarii (NTS) and in the paramedical reticular formation
of the medulla, especially in n. paramedian reticularis; a pauci-
synaptic “intermediate” response (1.7 msec mean latency) was
localized within the intermediate portion of the NTS; and poly-
synaptic “late” responses (peak > 5 msec) were found in specific
subnuclei of the medullary and pontine reticular formation. We
conclude that myelinated CSN fibers terminate in both the in-
termediate portion of the NTS and on large neurons of the paramedical
reticular formation of the medulla, that integration of CSN ac-
tivity occurs in the intermediate portion of the NTS, and that
specific reticular nuclei receive multisynaptic CSN projections.

chemoreceptor reflexes; reticular formation; baroreceptor reflexes;
central neural control of blood pressure

Recently Crill and Reis (17) discovered that primary af-
ferent fibers of the CSN could be excited antidromically
not only from the NTS but also from the medial reticular
formation in regions corresponding to the so-called de-
pressor centers of the medulla (1, 12). This observation
suggested a dual termination of CSN fibers in the brain
stem. Furthermore, it indicated a short pathway whereby
CSN activity could reach the medial reticular formation
since secondary projections from the NTS into this area in
the cat have not been found (37).

In order to ascertain if the primary afferent fibers de-
tected in both the NTS and the medial reticular formation
terminate in these regions, or are merely en passage, we
have recorded with microelectrodes the field and unit po-
tentials in the medulla and pons evoked by electrical stim-
ulation of CSN in the cat. A short-latency response which we
believe to be monosynaptic has been found in both the
NTS and the medial reticular formation. In addition, longer
latency polysynaptic projections have been identified in
specific nuclei of the medullary and pontine reticular forma-
tion. Preliminary reports of parts of this study have been
made (34-36).

METHODS

Adult cats were anesthetized by intravenous 1% alpha-
chloralose (35-55 mg/kg) after induction with ether.
After placement of arterial and tracheal cannulae, each
animal was placed in a stereotaxic frame with the head
flexed to 45°. The left carotid sinus nerve was approached
dorsolaterally (17) and placed on a bipolar platinum elec-

transducer and displayed on a channel of an Offner-
Harvard respirator pump. Systemic blood pressure was
recorded from the femoral catheter through a Statham P23a
transducer and displayed on a channel of an Offner-
Beckman polygraph, while heart rate, computed from the

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CAROTID SINUS NERVE IN CAT BRAIN STEM

Fig. 1. Distribution of electrode penetrations projected onto floor of IVth ventricle of cat that were explored for responses evoked by electrical stimulation of ipsilateral carotid sinus nerve. Positive responses represented by open circles on left side of drawing; negative responses by solid circle on right. Shaded strip on right-hand side of drawing represents course of the nucleus tractus solitarii.

pressure pulse by a cardiotrachometer, was also displayed. End-expired CO₂ was recorded by a Beckman infrared CO₂ meter in order to maintain alveolar CO₂ in these paralyzed, artificially ventilated animals at constant levels of 2-3%.

The electrical stimulus of the CSN was a 0.1-msec pulse delivered from a Grass S4 stimulator through a Grass RF isolator to the animal. The stimulus current was amplified and constantly displayed on an oscilloscope by methods previously described (17). Recording electrodes were capillary-glass microelectrodes filled with 2 M NaCl and fast-green dye (59) for marking, and mounted in a Kopf microelectrode drive. Tip diameters ranged from 1 to 30 μ and tip resistances were around 1 megohm. Stereotaxic coordinates of the point of entry were determined visually with reference to the obex. The vertical reference was to the surface of the brain at the point of entry.

The conduct of the experiment was as follows: After establishing the viability of the CSN, the threshold current for the vasodepressor response was determined for a stimulus train (12-24 sec at 80 cycles/sec). The nerve was then repetitively stimulated at 0.5 cycle/sec at a stimulus intensity 5 times threshold while the brain stem was systematically explored from dorsum to base of brain. The evoked electrical responses were amplified by a Grass P5 cathode follower and preamplifier, the frequency band-pass of which was 0.3-2.0 kc, and displayed on the screen of a Tektronix model 565 oscilloscope. Positive tracks were those from which evoked potentials were recorded and were anatomically identified by depositing dye from the electrode at two levels with a d-c current (electrode negative) of 5-15 μA for 8-12 min. A negative track was one in which: 1) the viability of the CSN was established by demonstration of a reflex blood pressure response to electrical stimulation of the nerve; 2) evoked potentials were absent at stimulus intensities 5 times greater than the threshold for a vasomotor response; 3) the recording condition and electrodes were judged as adequate by detection of spontaneous discharges in neurons in the brain stem during the electrode penetration. Any penetration in which no evoked activity was seen but which failed to meet these three criteria was eliminated from the study. At the end of the experiment, the animal was perfused with 10% formaldehyde and the brain was fixed, frozen, and sectioned every 50 μ. The dye spots were located on unstained sections and the tracks reconstructed. Sections were then stained by the method of Kluver and Berrera (30) for further analysis.

RESULTS

A) Areas Explored

The distribution of electrode tracks from which potentials were evoked by stimulation of the ipsilateral CSN, projected onto the floor of the IVth ventricle, is illustrated in Fig. 1. Of the 362 satisfactory penetrations 164 were positive, although 33 are excluded from the study because the location of the electrode tip could not be identified; 198 tracks were negative.

Fig. 2. Histogram of distribution of early, intermediate, and late responses according to peak latency elicited by electrical stimulation of carotid sinus nerve.

inspection of Fig. 1 indicates that evoked potentials could be elicited from numerous loci within the medulla and pons. Many positive tracks were heavily concentrated in medulla over the NTS, particularly near the obex, but numerous positive tracks were found beyond the confines of this nucleus. Few positive tracks were observed behind the commissural nucleus. Contralateral responses were infrequent so their tracks are not indicated in this figure. Numerous negative tracks were located in regions in which positive responses were found in other experiments, indicating that responses evoked by CSN stimulation in the brain stem are somewhat inconstant from cat to cat.
Several types of evoked electrical responses were found. These were divided by the criterion of latency into three groups (Fig. 2): 1) a response with a peak latency less than 2 msec, the early response; 2) a response with a peak latency from 2 to 5 msec, the intermediate response; 3) responses with peak latencies greater than 5 msec, the late responses.

Evoked responses were segregated on the basis of peak rather than onset latency since in combined responses (cf.) the onset of the evoked waves could not always be determined. As will be shown, these three responses differed from each other in characteristics other than latency and appear to be generated by distinct neuronal mechanisms.

**B) Early Response**

The early response is a monophasic negative wave of smooth contour with an onset latency ranging from 0.7 to 1.4 msec and a peak latency from 1.1 to 2.0 msec, averaging 1.5 msec. A representative example of an early response is illustrated in Fig. 3A. Characteristically, the amplitude of the evoked response changes along a track; it never changes form. As the response approaches its maximum, the rising slope of the response becomes steeper. In four instances, a low threshold potential, less than 0.5 mv in amplitude, preceded the onset of the early response by 0.4 to 0.5 msec. An example is seen in Fig. 3B. The maximum amplitude of the early response was variable and at times very large. Although usually less than 0.5 mv, in 10% of cases it ranged between 10 and 20 mv. The duration of the response ranged from 0.5 to 3.5 msec. Spontaneously discharging units were never locked into the evoked response nor could unit activity be discerned in the potential.

With repetitive stimulation, the early response fell to 50% of maximum amplitude (the f50) at frequencies below 200 cycles/sec, 58% having a f50 below 100 cycles/sec, the remainder ranging between 100 and 200 cycles/sec. The early response disappeared following 45 sec or less of hypoxia induced by shutting off the artificial ventilation in paralyzed cats and also after 5 mg/kg of intravenous pentobarbital.

The stimulus threshold for the early response is at, or just near, the threshold for the blood pressure response to electrical stimulation of the CSN. With increasing stimulus intensities, the evoked early response increases in amplitude up to stimuli 5 times threshold and then reaches a plateau.

The field of the early response ranged vertically from 0.3

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**Figures**

- **Fig. 3A**: early response elicited by electrical stimulation of carotid sinus nerve recorded at different depths from floor of IVth ventricle within medial reticular formation of medulla. Each oscilloscope tracing in this and subsequent illustrations, unless otherwise indicated, is superimposition of 10-20 sweeps (0.5 cycle/sec). Bottom trace is stimulus artifact. B: early response and a small antecedent potential, probably a fiber response, evoked by stimulation of carotid sinus nerve and recorded in medial reticular formation. Note early response does not appear at threshold for antecedent evoked response. Onset latency of antecedent potential is 0.6 msec and of early response 1.0 msec.

- **Fig. 4**: relationship between depth of electrode penetration in medulla, amplitude, and peak latency of early response. Open circles correspond to points along electrode track at same depth. Solid circle represents maximum response. Graph on left in this figure is a plot of amplitude of response, expressed as a percent of maximum response, as a function of electrode depth. Second graph plots peak latency expressed as a percent of maximum response as a function of electrode depth. Abbreviations as in Fig. 5.
FIG. 5. Distribution of responses recorded ipsilaterally evoked by electrical stimulation of carotid sinus nerve of cat. Tracks are projected onto 2 representative sections of medulla, row A lying 1.0 mm behind and row B 0.5 mm ahead of obex. Column 1: early responses (circles); column 2: intermediate responses (triangles); column 3: late responses (squares). In this and all subsequent illustrations, vertical lines represent electrode tracks and horizontal bar at bottom of each line represents extent of penetration. Solid symbols represent maxima responses in each track. Open symbols above and below the maxima represent extent of field. Abbreviations according to Taber (58): A: nucleus ambiguous; Ap: area postrema; Cd: nucleus medullae oblongatae centralis, subnucleus dorsalis; Cl: nucleus cuneatus lateralis; Cm: nucleus cuneatus medialis; Cv: nucleus medullae oblongatae centralis, subnucleus ventralis; G: nucleus gracilis; Ge: nucleus gigantocellularis; Ge: nucleus tractus solitarii, subnucleus gelatinous; Ic: nucleus intercalatus; Lrm: nucleus lateralis reticularis, subnucleus dorsalis; Lrs: nucleus lateralis reticularis, subnucleus subtrigeminalis; Olh: nucleus olivaris inferior accessorius dorsalis; Olm: nucleus olivaris inferior accessorius medialis; Olp: nucleus olivaris inferior principalis; Od: nucleus olivaris superior lateralis; Oim: nucleus olivaris superior medialis; P: nucleus parvoacellularis; Pmd: nucleus paramedian reticularis, subnucleus dorsalis; Pmv: nucleus paramedian reticularis, subnucleus ventralis; Pp: nucleus pontis centralis caudalis; Ppr: nucleus praepositus hypoglossi; Pyr: tractus pyramidalis; Rm: nucleus raphe magnus; Rob: nucleus raphe obscurus; Rpa: nucleus raphe pallidus; S: nucleus tractus solitarii; T1: nucleus trapezoidalis lateralis; Tm: nucleus trapezoidalis medialis; Ts: tractus solitarius; V: nucleus nerve trigemini; V1: nucleus tractus spinalis trigemini oralis; V2: nucleus tractus spinalis trigemini interpolaris; VIII: nucleus vestibularis lateralis; VIII1: nucleus vestibularis medialis; X: nucleus nervi vagi dorsalis motorius; XI: nucleus nervi hypoglossi.

from the point of maximum response. This conduction velocity is similar to that of dendrites (14).

The distribution of all early responses recorded in this study is shown in Fig. 5, superimposed on representative sections of the cat brain just ahead and behind the obex. The maxima (indicated by solid circles in Fig. 5, A1 and B1) of 25 (or 72%) of the 32 positive responses were localized to the medullary reticular formation; 16 (or 50%) of the total were localized in an area corresponding to the nucleus paramedian reticularis and 7 (or 22%) to portions of the dorsolateral reticular formation. (In this paper, brainstem nuclei are identified by the terminology of Taber (58).) Nine (or 28%) of the responses were localized in or adjacent to the NTS. The reticular responses were equally distributed in an area running from 1 mm ahead to almost 1 mm behind the obex. The remaining responses tended to lie medially. No contralateral responses were observed.

The brief latency of the early response indicates that it must arise either from neurons excited monosynaptically...
TABLE 1. Characteristics of intermediate response evoked by electrical stimulation of carotid sinus nerve and recorded ipsilaterally in medulla of the cat

<table>
<thead>
<tr>
<th>Form</th>
<th>Negative-positive, or positive</th>
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<tbody>
<tr>
<td>Localization</td>
<td>Negative wave: ventromedially in intermediate portion of NTS</td>
</tr>
<tr>
<td></td>
<td>Positive wave: adjacent to intermediate portion of NTS</td>
</tr>
<tr>
<td>Latency, msec</td>
<td></td>
</tr>
<tr>
<td>Onset: mean ± se</td>
<td>1.7 ± 0.4 range: 1.0-2.8</td>
</tr>
<tr>
<td>Peak: mean ± se</td>
<td>2.9 ± 0.6 range: 2.0-4.3</td>
</tr>
<tr>
<td>Duration, msec</td>
<td></td>
</tr>
<tr>
<td>Mean ± se</td>
<td>3.9 ± 2.9 range: 1.6-9.9</td>
</tr>
<tr>
<td>f&lt;sub&gt;0&lt;/sub&gt;, cycles/sec</td>
<td>Negative wave: &lt;40</td>
</tr>
<tr>
<td></td>
<td>Positive wave: &lt;10</td>
</tr>
<tr>
<td>Stimulus intensity for maximal response (X threshold)</td>
<td>5</td>
</tr>
<tr>
<td>Unit activity</td>
<td></td>
</tr>
<tr>
<td>Negative wave</td>
<td>abundant</td>
</tr>
<tr>
<td>Positive wave</td>
<td>none</td>
</tr>
</tbody>
</table>

(i.e., postsynaptically) by primary afferent fibers of the CSN or presynaptically from the afferent fibers themselves. That the response is postsynaptic can be adduced from the following lines of evidence:

1) Location. The location of the early response in a limited area of the NTS near the obex corresponds to the location of the neurons in the nucleus upon which CSN fibers are believed to terminate (15, 28, 48). On the other hand, the early response is not found in penetrations through the rest of the NTS and tractus solitarius from the root entry of the IXth nerve, 4 mm rostral to the obex (15, 17), and through its pathway caudally to points at least 4 mm behind the obex. If early responses originated in CSN fibers, one would expect to find them throughout the course of this afferent path.

2) Configuration. The persistently negative configuration of the early response, which never changes its form along an electrode track, is compatible with the field around some neurons excited monosynaptically (39). It is unlike the usual polyphasic tract response recorded centrally from entering fibers of other cranial nerves such as the trigeminal (19) and vestibular (43).

3) Properties of the field. The shift of the peak latency as a function of distance along an electrode tract, a characteristic of the early response, is not a property of the fields recorded perpendicularly to nerve tracts in the brain, such as the pyramidal tract (42). It is, however, compatible with a response arising from neurons either in aggregate, as in the oculomotor nucleus (32), hippocampus (16), and cerebral cortex (13), or from single spinal motoneurons (39).

4) Latency. The latency of the onset and peak of the early response is 0.4-0.5 msec longer than the comparable latencies for the action potential elicited antidromically by stimulation of CSN fibers in the medulla and recorded peripherally in CSN (17). Hence it is compatible with a delay across one synapse (22).

5) Response to repetitive stimulation. The early response attenuates at considerably lower frequencies of repetitive stimulation than does the antidromic CSN response (which has a f<sub>0</sub> around 800 cycles/sec (17)). This would be expected assuming the early response is a postsynaptic response.

6) Effect of hypoxia and barbiturates. The early response has a greater sensitivity to hypoxia and barbiturates than the antidromic response, as would be expected if the early response were postsynaptic (50). With hypoxia the early response is abolished within 45 sec while the antidromic fiber response persists for at least 2 min (17). Likewise, the early response is abolished by amounts of barbiturates which do not affect the antidromic CSN response (17).

7) Prepotentials. A lower threshold negative wave was seen to precede the early response by 0.4-0.5 msec, suggestive of presynaptic activity in entering rootlets. No potentials ever preceded the antidromic responses. Hence we may conclude that the early response is a monosynaptic reflex elicited by electrical stimulation of the CSN.

Assuming a synaptic delay of 0.4 msec and a mean conduction distance along the CSN to the recording electrode of 27 mm, the conduction velocity of fibers triggering the early response would range from 90 to 27 m/sec, which on conversion to fiber diameter would indicate all to be myelinated fibers. This conclusion is supported by the fact that the maximum amplitude of the early response is reached with stimulus intensities only 5 times threshold for the vasodepressor response, well below the intensity required for

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![Fig. 6. Representative intermediate responses recorded from an electrode track passing laterally to and one penetrating nucleus tractus solitarius. It may be noted in this track that at 1.0 mm from surface, response appears as a purely negative wave (subsequent to small antecedent hump of an early response) with a peak latency of 2.8 msec. As electrode reaches 1.3 mm, a positive wave of shorter peak latency (2.0 msec) appears, and at 1.6 mm it is dominant feature of the response, persisting until response disappears several hundred micra farther down track (not shown). Positive response is seen only when electrodes pass through or near the ventromedial portion of NTS, suggesting it is generated by neurons in this region. Abbreviations as in Fig. 5.](http://ajplegacy.physiology.org/10.1152/ajplegacy.1975.50.1.146.2.20.3.4)
The intermediate response consists of a polyphasic potential which, in contrast with the early response, changes its shape as well as its size along an electrode track. The vertical extent of the field of the intermediate response is smaller than that of the early response and no shift of the latency of any components is seen as the track progresses through the brain. Some characteristics of this response are indicated in Table 1. It is recorded primarily from a region running from 0.5 mm behind to 2.0 mm rostral to the obex, in most instances in close relationship to the NTS (Fig. 5, A2 and B2) and is probably identical with the NTS field responses reported by Humphrey (25). The largest and most characteristic form of the response is a negative-positive wave which is recorded within the NTS, in the intermediate portion of the nucleus. A typical example is represented by the medial track illustrated in Fig. 6. Responses recorded medial to the NTS are similar in form and latency to responses recorded in the nucleus itself but are of smaller amplitude, suggesting they are volume conducted. With tracks passing lateral to the NTS, the responses are primarily negative; the only suggestion of the positive is a perceptible break in the rising slope of the potential. It is probable, as Humphrey has suggested (25), that the positive and negative components of the intermediate response arise from different neural generation since the localization of each wave, the $f_{30}$, and density of the associated unit activity differ for each.

The several intermediate responses recorded in the medial reticular formation were always negative in configuration and associated with units. They probably represent rare examples of responses generated by neurons of the reticular formation, with peak latencies less than 5 msec (see below).

The intermediate response was preceded by an early response in about half of the positive tracks. An example is seen in Fig. 7. The two responses, however, could be distinguished not only by form and latency but also by a spatial separation of their respective maxima, which again suggests different origins of the early and intermediate responses.

The threshold stimulus intensity during an intermediate response to CSN stimulation was close to that eliciting a reflex fall in blood pressure. With increasing stimulus intensities, a maximal evoked response was reached with stimuli less than 5 times threshold. Thus, it appears that the same fiber population in CSN initiates both the early and intermediate responses and that the bulk of these fibers is myelinated. Since both responses are triggered by CSN fibers of similar size, the longer latency of the intermediate complex cannot be ascribed to a slower conduction velocity of afferent fibers evoking the response but must mean that the intermediate response is polysynaptic. However, since the latency differences for the two responses range from 0.4 to 1.4 msec, it is probable that many of the intermediate responses are di- and at most trisynaptic.

D) Late Responses

The late responses are polysynaptic potentials evoked in medulla and pons by CSN stimulation which have peak latencies ranging from 5 to over 80 msec (Fig. 2). In addition to a longer peak latency, late responses differ from the early and intermediate responses by a) a prolonged duration, b) a slower rise and decay of the evoked potentials, c) an $f_{30}$ usually less than 20 cycles/sec with the exception of the

FIG. 7. Early (circle) and intermediate (triangle) responses evoked by electrical stimulation of carotid sinus nerve recorded along a single electrode track in medulla at different depths. Graph plots amplitude responses as percent of maximum at different depths. Solid symbols represent maxima. Note that intermediate response appears above NTS at its commissural portion and within NTS consists of a small positive and larger negative wave, both of which disappear below nucleus. Within nucleus a shorter latency (peak 1.4 msec) early response appears which reaches its maximum within underlying reticular formation and disappears with further penetration into brain. Larger field and gradual shift of peak latency in early response as maxima are approached is seen in this illustration in contrast with smaller field and fixed latency of intermediate response.

FIG. 8. Distribution of late responses recorded in pons of cat elicited by electrical stimulation of carotid sinus nerve and displayed on a representative section taken through middle of superior olivary nucleus. Symbols and abbreviations as in Fig. 5.
TABLE 2. Characteristics of late responses evoked by electrical stimulation of carotid sinus nerve and recorded ipsilaterally in different nuclei of medulla and pons of cat

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Preponderant Form</th>
<th>N</th>
<th>Latency, msec*</th>
<th>Duration, msec*</th>
<th>f50 cycles/sec</th>
<th>Stimulus Intensity for Maximal Response (X threshold)</th>
<th>Unit Activity</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Onset</td>
<td>Peak</td>
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<tr>
<td>Medulla</td>
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</tr>
<tr>
<td>Pmd</td>
<td>Positive</td>
<td>6</td>
<td>3.8±2.3</td>
<td>12.0±0.5</td>
<td>19.4±4.6</td>
<td>&lt;40</td>
<td>5</td>
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<tr>
<td></td>
<td>(1.5-7.0)</td>
<td></td>
<td>(11.3-12.5)</td>
<td>(10.5-23.0)</td>
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<td></td>
<td></td>
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<tr>
<td>Pmv</td>
<td>Positive-negative</td>
<td>3</td>
<td>2.2±0.3</td>
<td>6.0±2.0</td>
<td>11.8±7.5</td>
<td>&lt;4</td>
<td>5</td>
</tr>
<tr>
<td>or negative</td>
<td></td>
<td>4</td>
<td>11.3±9.3</td>
<td>36.6±28.0</td>
<td>64.0±67.1</td>
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<tr>
<td></td>
<td>(3.0-21.0)</td>
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<td>(9.0-73.0)</td>
<td>(10.0-157.0)</td>
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<tr>
<td>Cdv, Cvn</td>
<td>Negative</td>
<td>17</td>
<td>3.9±2.4</td>
<td>8.2±1.8</td>
<td>16.9±8.7</td>
<td>&lt;20</td>
<td>5-10</td>
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<td>(1.8-12.5)</td>
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<td>(6.0-11.5)</td>
<td>(9.2-37.5)</td>
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<td></td>
<td></td>
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<tr>
<td>Rob</td>
<td>Positive-negative</td>
<td>5</td>
<td>5.2±0.7</td>
<td>11.5±3.3</td>
<td>19.5±11.4</td>
<td>&lt;10</td>
<td>&lt;20</td>
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<tr>
<td>or negative</td>
<td></td>
<td></td>
<td>(4.5-5.5)</td>
<td>(8.0-16.0)</td>
<td>(8.0-38.5)</td>
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<td></td>
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<tr>
<td>Rpa</td>
<td>Positive-negative</td>
<td>4</td>
<td>19.6±5.0</td>
<td>47.6±16.8</td>
<td>57.5±4.9</td>
<td>&lt;10</td>
<td>&lt;20</td>
</tr>
<tr>
<td>or negative</td>
<td></td>
<td></td>
<td>(12.5-23.0)</td>
<td>(27.5-62.0)</td>
<td>(52.0-63.0)</td>
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<tr>
<td>Pons</td>
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<td></td>
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<tr>
<td>Poc Ge</td>
<td>Negative</td>
<td>20</td>
<td>6.5±3.9</td>
<td>23.9±25.1</td>
<td>41.4±46.3</td>
<td>&lt;20</td>
<td>&gt;20</td>
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<tr>
<td></td>
<td>(4.3-19.5)</td>
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<td>(6.0-90.0)</td>
<td>(6.3-153.0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pc</td>
<td>Negative</td>
<td>8</td>
<td>4.5±0.5</td>
<td>9.7±1.8</td>
<td>25.7±2.2</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4.0-5.0)</td>
<td></td>
<td>(8.0-13.5)</td>
<td>(9.0-65.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rob</td>
<td>Positive-negative</td>
<td>5</td>
<td>11.1±2.3</td>
<td>16.3±3.0</td>
<td>17.1±6.7</td>
<td>&lt;6</td>
<td>&gt;20</td>
</tr>
<tr>
<td>or negative</td>
<td></td>
<td></td>
<td>(7.5-13.5)</td>
<td>(12.0-90.0)</td>
<td>(12.5-38.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Km</td>
<td>Positive-negative</td>
<td>7</td>
<td>17.8±11.2</td>
<td>39.5±28.6</td>
<td>62.4±36.3</td>
<td>&lt;6</td>
<td>&gt;20</td>
</tr>
<tr>
<td>or negative</td>
<td></td>
<td></td>
<td>(5.0-37.0)</td>
<td>(7.0-100.0)</td>
<td>(6.5-103.0)</td>
<td></td>
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</tr>
</tbody>
</table>

For abbreviations see Fig. 5. * Values are means ± se with ranges given in parentheses.

late responses of the dorsal paramedian region, d) abundant associated unit activity, e) contributions of high threshold CSN fibers to many of the evoked potentials.

The late responses were concentrated within the confines of specific nuclei of the reticular formation of the medulla and pons (Fig. 5, A3 and B3; Fig. 8). The characteristics of each of these responses within specific regions are tabulated in Table 2 while representative recordings are indicated in Figs. 9 and 10.

Late responses in medulla. Within the medulla the responses were concentrated, in agreement with Humphrey (25), in three principal areas: the region of the nucleus paramedian reticularis, the dorsolateral reticular formation comprising the nucleus medulla oblongata centralis, and the nuclei of the raphe.

Late responses recorded in the nucleus paramedian reticularis were primarily located within the dorsal subdivision of that nucleus in an area in which early responses were also frequently recorded. The late response in this region consisted of a positive wave often, but not invariably, preceded by an early response as illustrated in Fig. 9d. Since both the late and early responses recorded in the dorsal part of the nucleus paramedian reticularis are elicited by CSN fibers of the same threshold, the longer latency and f50 of the late response are probably due to polysynaptic delay of CSN evoked activity rather than slow conduction by small afferent fibers.
Late responses recorded in the nucleus medullae oblongatae centralis (Fig. 9D) were uniformly negative throughout the dorsal and ventral portions of the nucleus and usually were elicited in full by CSN fibers at stimulus intensities 5 times threshold. Occasionally, however, the evoked response in this region would increase with stimulus intensities up to 10 times threshold. The similarity of the latencies for late responses in the nucleus paramedian reticularis and in the lateral medulla suggests that both regions are excited by pathways from the CSN of approximately equal complexity.

The late responses of the raphe nuclei (Fig. 9B) differed from those of the paramedian and dorsolateral regions by having, in general, longer latencies, a lower f50, and having high threshold CSN fibers contribute to the evoked response. It is thus possible that both multiple synapses and slower conduction in CSN fibers contribute to the longer latency. While evoked slow waves and units were recorded in both the nucleus raphe obscurus and the nucleus raphe pallidus, both the amplitude of the evoked wave response and the density of the evoked unit activity were greater in the nucleus raphe obscurus.

Notable was the absence of evoked potentials in the dorsal motor nucleus of the vagus, and in the nucleus ambiguus. Evoked activity was rare in the inferior olivary nucleus and when it occurred consisted of field potentials without unit activity possibly volume conducted from adjacent regions.

Late responses in pons. In the posterior two-thirds of the pons, late responses were concentrated in a central tegmental area comprising the nucleus gigantocellularis, nucleus pontis centralis caudalis, and the nucleus parvo- cellularis, and also in pontine nuclei of the raphe.

The central tegmental responses were similar in configuration to those of the dorsolateral medullary region (Fig. 10, B, C, and D). Although the mean latencies of the pontine tegmental evoked responses were slightly longer than those recorded in the dorsolateral and paramedial regions of the medulla, some overlap was found (Table 2) suggesting that relays into the pontine tegmentum are not simply by an ascending polysynaptic route from the medulla.

The principal difference between the late responses recorded in the pontine tegmentum and those recorded in the medulla was in the stimulus intensities evoking the response. In the pons, the amplitude of the evoked response would continue to increase with stimuli up to and even greater than 20 times threshold (Fig. 11) in contrast to the medulla (excepting the raphe nuclei) where responses reached maxima at 5 times threshold. This suggests a convergence of input from both myelinated and unmyelinated CSN fibers into the central tegmental region of the pons.

The late responses recorded in the pontine raphe nuclei were similar in form to those of the medullary raphe nuclei.
As in the medulla, both amplitude and unit density were greater in the dorsally situated nucleus (n. raphe obscurus) than in the underlying nucleus (n. raphe magnus). The longer latency for the onset of evoked responses in the pontine raphe nuclei suggests that activity is ascending into the pons along a polysynaptic pathway from the raphe region of the medulla.

**DISCUSSION**

The identification of the early evoked response to electrical stimulation of the CSN as a monosynaptic reflex makes it possible to localize the regions of the brain stem in which the myelinated fibers of this nerve terminate. It appears that the CSN has a dual termination in brain stem, synapsing in both the NTS and in a paramedial zone of the medial reticular formation. The localization of evoked responses in these two regions indicates that the primary afferent fibers, antidromically excited from the same regions by Crill and Reis (17), indeed terminate there and are not merely en passant. Localization of terminations of fibers of the CSN in the NTS, particularly within the intermediate portion of the nucleus, confirms the speculation of anatomists (15, 28, 48).

On the other hand, discovery that CSN fibers project directly into the medial portion of the reticular formation had not been suspected. While projections from other cranial nerves into the reticular formation have been described (2, 47), our finding is, to our knowledge, the first electrophysiological demonstration of a monosynaptic connection between a peripheral nerve and reticular neurons.

Moresit (37) has recently shown that lesions of the posterior half of the NTS result in terminal degeneration in the dorsolateral but not medial parts of the medullary reticular formation. Since the medial reticular nuclei of the medulla appear to mediate the reflex depressor responses from the carotid sinus (62), Morest's observations leave unanswered the question of how impulses arising in the carotid sinus reach the medullary “depressor” areas. Our findings provide one answer by indicating a direct route with a high degree of synaptic security from CSN into the medial portions of the bulb.

The generator of the early response is uncertain. Because it is graded, it cannot represent the activity of single neurons recorded extracellularly. It could represent summation of postsynaptic potentials (PSPs) from several neurons without neuronal discharge or, alternatively, the action potentials of a packet of neurons discharging synchronously. The fact that no spontaneously active neurons could be locked into an evoked response, and the absence of discernible unit activity within the evoked wave, make it more likely that the early response consists of PSPs.

The small percentage of the field occupied by the maximal response, the apparent dorsoventral orientation of the field, and the prolongation of the peak latency suggest that after originating in a relatively concentrated area, the evoked activity spreads, primarily dorsoventrally, into extensive dendritic expansions of the excited neurons. There are neurons within this region of the reticular formation with morphological features which could serve as the likely source of the early responses. These neurons, described in detail by the Schciebs (54), are very large with dendritic fields oriented dorsoventrally and, in the kitten, extend almost from the floor of the IVth ventricle to the base of the brain. Individual dendrites of the large reticular neurons may be upward of 800 μ in length (60). Further studies with intracellular marking techniques may reveal if these large reticular neurons are indeed monosynaptically excited by stimulation of the CSN.

The CSN fibers terminating within the NTS initiate polysynaptic activity in adjacent portions of the nucleus that is reflected in the complex potential termed, in this study, the intermediate response. From our study it seems likely that CSN activity in the NTS does not spread into the rostral or caudal thirds of the nucleus but is highly localized to the intermediate portion. This fact is in concordance with the
observations that those parts of the NTS involved in cardio-pulmonary regulation are probably distinct from those portions of the NTS mediating taste sensation (47) or modulating the activity of the mesencephalic reticular formation as described by Bonvallet and Allen (6). Several neural elements within the nucleus appear involved in the genesis of the potential. This suggests that a degree of integration for carotid baro- and/or chemoreceptor reflexes takes place in the NTS before further relay into the reticular formation.

Ultimately all CSN fibers project into the reticular formation of the medulla and pons. With the exception of the direct projections into the paramedial zone, these pathways for the complex potentials of the intermediate responses are polysynaptic and are localized to specific, albeit varied, nuclear areas.

In the medulla, the area of greatest interest lies in a paramedial zone lying at and ahead of the obex and encompassing for the most part the nucleus paramedian reticularis. Carotid sinus nerve fibers project both mono- and polysynaptically into this area suggesting its importance in mediating CSN reflexes. Numerous investigations of this region using lesion methods or electrical stimulation have indicated its paramount importance in cardiovascular reflex regulation. The region lies within the center of the so-called depressor area of the medulla (1, 12, 62). Furthermore, the integrity of this paramedial area appears necessary for sustaining the vasomotor components of the carotid sinus reflex (31, 55, 62), the depressor responses elicited by electrical stimulation of forebrain (31) and muscle nerves (24), and some of the cardiovascular responses elicited from cerebellum (36). Anatomically, this region receives innervation from mesencephalon, hypothalamus, spinal cord (9, 56), and a dense projection from cerebellum, particularly the fastigial nucleus via the fastigiobulbar tract (9, 55). The intermingling of terminal fibers from CSN with those from upper brain stem and cerebellum in this region suggests that the paramedial zone may be an important site wherein baroreceptor reflexes (and/or chemoreceptor reflexes) may be modulated by activity emanating from cerebellum (38, 46), forebrain (45), and other rostral areas of the brain.

The other regions of the medulla receiving polysynaptic projections from the CSN are the dorsolateral region of the reticular formation, encompassing the nucleus medullar oblongatae centralis and the raphe nuclei. Carotid sinus nerve activity is probably related to the dorsolateral area in the secondary projections from the NTS described by Morest (37). This pathway may be of importance in mediating the CSN effect on antidiuretic-hormone release (49, 55) and also its EEG-synchronizing action (7, 33). The pathway to the raphe nuclei is obscure but could possibly be lateral to medial reticular areas by a path described by Brodal (8). Since the raphe nuclei appear to play an important role in maintaining sleep (27), the CSN-raphe projection may serve to mediate the effects of the carotid sinus and carotid body on sleep and wakefulness (3, 4).

That the CSN projects above the medulla into the pontine tegmentum has been demonstrated for the first time in this study, a finding not surprising in view of CSN modulation of hypothalamic function and the EEG (7, 33, 49, 55). It is possible that this ascending pathway may relay CSN activity to some of the “cardiovascular” neurons in the pons and upper brain stem whose activity is modulated by the blood pressure. In accord with anatomical data (37) the pontine projections of CSN are polysynaptic, a fact which adds substance to the view that the principal neurons underlying at least one of the reflex functions of CSN, the vasomotor component of the baroreceptor reflexes, are located in the medulla wherein they may be modulated by suprasegmental brain areas (12, 45, 46).

It is not possible in this study to state whether the regions of medulla and pons demonstrated to receive projections from the CSN are exclusively concerned with either the baro- or chemoreceptor reflexes. However, although chemo- and baroreceptor afferent fibers are represented in both the myelinated and unmyelinated fibers in the CSN, the baroreceptors are particularly well represented among the largest myelinated fibers (21, 41). Since the evoked responses to CSN stimulation were always elicited by myelinated fibers and the blood pressure response to CSN stimulation was usually depressor, it is likely that those regions of brain stem in which CSN activity was recorded receive innervation from carotid baroreceptors with some as yet undetermined contribution from carotid body chemoreceptors.

In summary (see Fig. 12), we conclude that myelinated fibers of the CSN have a dual termination in brain stem ending in both the intermediate portion of NTS and a paramedial zone of the medullary reticular formation encompassing primarily the nucleus paramedial reticularis. In the NTS there are local polysynaptic circuits with subsequent polysynaptic relays into specific regions of the medullary and pontine reticular formation. These specific reticular regions therefore must be concerned with integrating activity arising from the baroreceptors of the carotid sinus and chemoreceptors of the carotid body into a wide range of reflex activities which seem to modulate visceral and behavioral activity of the organism.

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M. Miura is on leave from the Dept. of Physiology, Chiba University School of Medicine, Chiba, Japan.

Address reprint requests to: D. J. Reis, Dept. of Neurology, Cornell Medical Center, 525 East 68th Street, New York City 10021.

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