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# STUDIES ON THE EXCITABILITY OF SINUS NERVE AFFERENT TERMINALS

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SUMMARY

1. The excitability of sinus nerve afferent terminals within the nucleus of the tractus solitarius has been studied in cats and rabbits using the technique of antidromic activation.

2. Conditioning stimuli to the hypothalamic defence area increased the excitability of some glossopharyngeal nerve afferents, though no such effects were observed on sinus nerve terminals.

3. Although the excitability of superior laryngeal nerve afferent terminals was observed to fluctuate in phase with the central respiratory cycle, no equivalent variations in sinus nerve terminal excitability were observed.

4. It is concluded that sinus nerve afferent terminals are not influenced by presynaptic mechanisms. Possible sites for the observed modulations of baroreceptor and chemoreceptor reflexes are disscused in the light of these results.

## INTRODUCTION

It has been shown that during stimulation of the hypothalamic defence area both cardiac and vascular components of the baroreceptor reflex are effectively suppressed (Hilton, 1963, 1965; Coote, Hilton & Perez-Gonzalez, 1979). A study by McAllen (1976) has suggested that this results, at least in part, from a block of the baroreceptor input to neurones close to the first synapse in the baroreceptor reflex pathway. In addition, Weiss & Crill (1969) had earlier claimed to have demonstrated a primary afferent depolarization of sinus nerve terminals on stimulating in the fields of Forel. This would indicate that presynaptic mechanisms could modulate the excitability of these afferent terminals and contribute to the observed suppression of the baroreceptor reflex during the defence reaction.

The baroreceptor reflex is also modified during the respiratory cycle. A brief stimulus to the carotid sinus baroreceptors only evokes a vagal bradycardia if it is timed to coincide with expiration, the equivalent stimulus given in inspiration being ineffective (see Koepchen, Lux & Wagner, 1961; Haymet & McCloskey, 1975). The chemoreceptor reflex is similarly affected; for carotid body chemoreceptor stimulation enhances inspiratory effort only if the stimulus is timed to occur during inspiration (Black & Torrance, 1967; Eldridge, 1972). Recent experiments have shown that inspiratory neurones of the nucleus of the tractus solitarius only receive an

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excitatory input from chemoreceptors during inspiration (Lipski, McAllen & Spyer, 1977). As this dorsal group of inspiratory neurones probably represents an earlier stage in the respiratory pathway than the lateral group of respiratory neurones (Merrill, 1975), and they are located close to where sinus nerve afferents terminate (Lipski, McAllen & Spyer, 1975; Jordan & Spyer, 1977*a*), it can be argued that the respiratory 'gating' of this input must be acting even earlier in the reflex pathway. Accordingly, it becomes a possibility that these effects involve respiratory-induced changes in the excitability of the terminals of chemoreceptor afferent fibres.

In order to assess whether changes in the excitability of sinus nerve terminals during the defence reaction and central respiratory cycling could account for the observed changes in the efficacy of these reflexes, we have used the technique described by Wall (1958) to determine the excitability of sinus nerve terminals in these two situations.

Preliminary accounts of this work have been communicated to the Physiological Society (Jordan & Spyer, 1977*b*, 1978*a*).

## METHODS

Experiments were performed on adult female cats (2·0–3·5 kg body weight) anaesthetized with α-chloralose (B.D.H., 70 mg/kg) after induction with ethyl chloride and ether, and on New Zealand white rabbits (2·0–4·0 kg body weight) anaesthetized with ethyl carbamate (Urethane, Fisons Ltd, 1·5 g/kg). In all cases the anaesthetic was supplemented, if and when necessary, by small doses of pentobarbitone sodium (Sagatal, M & B Ltd, 2–3 mg/kg) given via cannula in a femoral vein. In all experiments a tracheostomy was performed low in the neck and both femoral arteries were cannulated. One cannula allowed blood pressure to be monitored continuously whilst the other enabled blood to be taken in order to monitor (Micro-Astrup) and maintain the [$HCO_3^-$] of the arterial blood within physiological limits by the administration of $NaHCO_3$. Rectal temperature was maintained at 37·5 ± 0·5 °C with a heating blanket.

The sinus and glossopharyngeal nerves on one side were prepared using a lateral approach (Jordan & Spyer, 1977*a*). In some experiments the superior laryngeal nerve was identified anatomically where it joins the nodose ganglion and a length dissected clear for recording. Bipolar silver wire electrodes were used to record activity in the central ends of the cut nerves, peripheral to the junction of the sinus and glossopharyngeal nerves. The medulla was exposed by a dorsal approach and penetrated with monopolar tungsten electrodes (impedances 20–60 kΩ measured at 1 kHz) to locate sites from which antidromic activity in the nerves could be evoked. When a responsive area was located, the threshold for a single response was determined at different depths during each penetration to enable depth-threshold contours to be constructed. 'Field' contours, which we interpret as reflecting terminal arborizations (Jordan & Spyer, 1977*a*; Lipski *et al.* 1975; McAllen, Jordan & Spyer, 1979) were located in the vicinity of the nucleus of the tractus solitarius, 0–3·0 mm rostral to the obex. Many individual responses were averaged using a signal averager (Ortec 4620 + 4623).

### *Defence area experiments*

These experiments were performed on nineteen cats. For stimulating the hypothalamic defence area, the skull was opened using a dental drill, the exposed edges being sealed with bone wax and the dura incised and reflected. The left renal nerves were isolated retroperitoneally. The nerves selected for use were cut and the central ends placed on a pair of bipolar silver wire electrodes. The activity from these nerves was amplified, rectified and smoothed before being displayed on a pen recorder.

Using a digitimer and isolated stimulator (Devices Ltd), trains of 0·1–1·0 msec pulses at 50–200 Hz and intensities 10–25 V were applied to the hypothalamus via a stereotactically placed bipolar concentric steel electrode (David Kopf, SNE 100, impedence 25–50 kΩ measured

at 1 kHz). The electrode was advanced until stimulation evoked the autonomic components of the defence reaction (Abrahams, Hilton & Zbrożyna, 1960). Guided by the changes evoked in renal nerve activity, heart rate and arterial blood pressure, the electrode was finely moved until hypothalamic stimulation could completely suppress the responses evoked by electrical stimulation of the sinus nerve. At this point, the animals were paralysed with gallamine triethiodide (Flaxedil, M & B Ltd, 3–4 mg/kg) and artificially ventilated, end-tidal $P_{Co_2}$ being continuously monitored using a medical gas analyser (Beckman, type LB1).

After recording test responses in the glossopharyngeal and sinus nerves to the medullary stimulus alone, conditioning stimuli were applied to the hypothalamic defence area such that the conditioning stimuli ended 0–2500 msec prior to the medullary stimuli. In some experiments picrotoxin (Fluorochem Ltd, 1·0 mg/ml.) in doses of up to 1·5 mg/kg were given intravenously.

*Respiratory experiments*

These experiments were performed on nine rabbits and six cats. The right phrenic nerve was exposed low in the neck and cut distally. Spontaneous activity, recorded with bipolar silver wire electrodes was amplified, rectified and smoothed before being displayed on a pen recorder. A comparator was used to provide a trigger signal at the onset of the rise in the rectified phrenic signal, this signal being used to start the digitimer cycle. By delaying the stimulus from the start of the digitimer cycle, the medullary stimulus could be applied at any time during the respiratory cycles. Antidromic activity in the sinus or superior laryngeal nerve could thus be evoked and averaged at different phases of the central respiratory cycle.

*Histology*

At the end of each experiment the brain was removed and fixed for several days in 10% formal saline. Frozen sections 50 $\mu$m thick were cut and stained with neutral red. The exact locations of the sites of stimulation were determined as described previously (Lipski *et al.* 1975).

## RESULTS

### *1. Presynaptic effects of defence area stimulation*

Having located a site within the 'defence area' which would abolish the responses to sinus nerve stimulation (Coote, Hilton & Perez-Gonzalez, 1979), antidromic mass activity in the sinus and glossopharyngeal nerves was evoked by microstimulation within the medulla at twice threshold intensity (Jordan & Spyer, 1977*a*; McAllen *et al.* 1979). Since this value always gave a submaximal response, the magnitude of the potential could then either increase or decrease if the excitability of the terminals changed. These responses (test responses) were recorded and averaged and the averaged value compared with similarly evoked averaged responses to a medullary stimulus preceded at various intervals by a conditioning stimulus to the 'defence area' (usually a 100 msec train of 1 msec pulses at 70–100 Hz). A typical recording from the glossopharyngeal nerve during such a protocol can be seen in Fig. 1*A*. Each trace represents the averaged response to sixteen individual stimuli delivered to the medulla (*T*, test response) or preceded by hypothalamic conditioning stimuli. Both the amplitude and width of the evoked responses increased when a conditioning stimulus preceded the test stimulus.

From the same medullary site of stimulation, activity was also evoked in the sinus nerve (Fig. 1*A*), but the magnitude of this response was largely unaffected by a conditioning stimulus to the hypothalamus. To quantify the effect, the area of the averaged, evoked responses were measured and plotted as in Fig. 1*B*. The ordinate shows the area of each averaged conditioned response as a percentage of its averaged

test responses. The interval between the conditioning and test stimuli is shown on the abcissa. It is obvious from this plot that there is a marked facilitation of the glossopharyngeal evoked response over condition-test intervals of 100–1100 ms, the maximum increase of 51% being at about 100 msec. However, the sinus nerve responses, although varying about the 100% mark, were not different ($P < 0{\cdot}05$; using a statistical test of variance) from this line, the largest change being 10%.

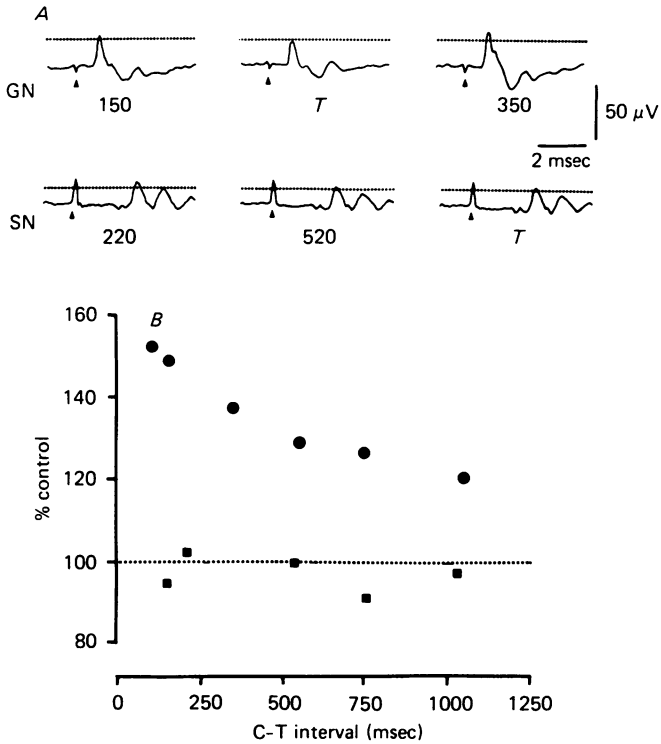


Fig. 1. Cat. Effect of conditioning stimuli in the hypothalamic defence area on the antidromically recorded potentials in the glossopharyngeal (GN) and sinus (SN) nerves. In *A* each trace is an average of sixteen medullary stimuli (0·1 msec pulses 30 μA given at ▲, 1 every 30 sec). Traces marked *T* are those evoked by stimulation of the medulla alone whilst the figures indicate the interval between the end of the conditioning stimulus to the hypothalamus (100 msec train, 1·0 msec pulses at 100 Hz, 20 V) and the medullary stimulus. *B*, a quantitative assessment of the effect of a defence area conditioning stimulus on the antidromic responses recorded in glossopharyngeal (●) and sinus nerves (■). The ordinate shows the area of the conditioned response as a percentage of the area of its nearest test response. On the abscissa is plotted the interval between the conditioning stimulus and the test medullary stimulus.

Although in theory the antidromic stimulation technique appears relatively simple and convenient to use, in practice there are several inherent problems with it, the most serious being the prolonged time required to obtain a complete set of data. Unless the recording situation is stable over a long period, any change in the magnitude of the potentials during conditioning may go unnoticed. This can, in part, be remedied by 'bracketting' every conditioned response with test responses. In the experiments described in this paper the condition-test regime was repeated only at

a very slow rate (usually 2–4/min) since defence area stimulation will evoke pressor responses which are, however, insignificant if the stimuli were applied at this very low rate. This, however, extends even further, the time required to collect the data and makes it difficult to perform complete runs on each evoked potential.

TABLE 1. Results of various condition-test intervals on thirteen sinus nerve potentials

| | Increased ($n$, latency range) | Decreased | No change | Total |
|---|---|---|---|---|
| Glossopharyngeal nerve potentials | 8, 0·8–3·0 msec | 0 | 9, 0·7–1·9 msec | 17, 0·7–3·0 msec |
| Sinus nerve potentials | 0 | 4, 1·4–3·6 msec | 9, 0·9–20·0 msec | 13, 0·9–20·0 msec |

The results of the present experiments are summarized in Table 1. In these experiments we report on thirteen sinus nerve potentials which were subjected to a range of condition-test intervals; of these nine were unaltered. This was also the case for the potentials ($n$ = 8) on which only one condition-test interval was investigated. In no case was the size of a sinus nerve potential increased, though on four occasions a decrease in the magnitude of the potentials was observed which may indicate a presynaptic hyperpolarization of sinus nerve terminals. However, these potentials were recorded in preliminary experiments and it was noted that in each case of suspected primary afferent hyperpolarization there was also a concomitant rise in arterial blood pressure. Thus, the change in the size of the response may have been due to movements of the electrode in relation to the brain, since noradrenaline-induced blood pressure rises caused marked decreases in the size of the evoked potentials. In contrast, however, of the seventeen glossopharyngeal potentials subjected to a range of hypothalamic condition-test intervals, only nine were unaltered whilst the remaining eight all showed marked increases in the size of the potential, suggesting a primary afferent depolarization of their terminals. This effect was most marked over condition-test intervals of 100–200 msec and often lasted up to 2000 msec. On several occasions ($n$ = 18) evoked potentials were tested with only one condition-test interval. These showed similar effects to those described above, some increasing in magnitude ($n$ = 5) whilst others were unaltered ($n$ = 13). In the present description we only include those sinus nerve responses recorded in experiments in which at least one of the glossopharyngeal potentials showed a positive effect since such trials are the only ones which are valid for the interpretation of the negative data provided here.

The present experiments have confirmed that focal stimulation of the 'defence area' can suppress the effects of sinus nerve stimulation, but it does not appear that this effect is the result of a presynaptic modulation of sinus nerve terminals as suggested by Weiss & Crill (1969). This negative result was obtained despite positive results recorded from the glossopharyngeal nerve where changes in excitability consistent with primary afferent depolarization were noted. Further evidence that the changes in the glossopharyngeal potential were indicative of primary afferent depolarization were found in experiments in which picrotoxin, a GABA antagonist,

was administered. This has been shown to depress presynaptic inhibition in the spinal cord (Schmidt, 1963) and brainstem (Banna & Jabbur, 1969). Indeed, a dose of 0·5 mg/kg given intravenously abolished the effects of a defence area conditioning stimulus on the glossopharyngeal evoked potential.

*2. The modulating effects of central respiratory activity*

The possibility that the respiratory modulation of baroreceptor and chemoreceptor reflexes is a result of presynaptic inhibition of primary baroreceptor and chemoreceptor afferents has been tested. If it were so, then sinus nerve terminals ought to show a respiratory variation in their excitability.

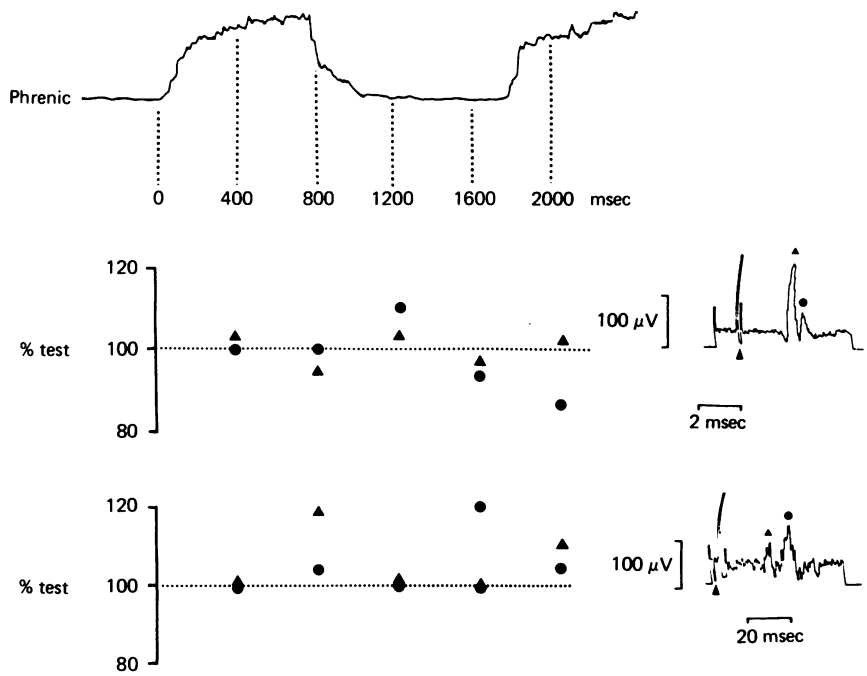


Fig. 2. Rabbit. The effect of respiration on the excitability of sinus nerve terminals. Upper trace shows activity recorded in the phrenic nerve, rectified and smoothed. Lower plots show the area of each evoked response as a percentage of the area of the response evoked at the onset of the rise in phrenic activity (time 0). On the abscissae are plotted the intervals between the onset of the rise in phrenic nerve activity and the medullary stimuli. Each trace shows an average of the responses evoked by sixteen medullary stimuli (0·1 msec pulses, 10 μA given at ▲ every 3·5 sec) at time 0.

Since the animals were paralysed and artificially ventilated, phrenic nerve activity (rectified and smoothed) was used as a monitor of central respiratory activity. By triggering the Digitimer at the onset of the rise in phrenic nerve activity, averaged evoked responses in the sinus nerve could be recorded at any present time during the respiratory cycle.

Twelve antidromically evoked sinus nerve potentials (latencies 2·5–35 msec) were investigated in rabbits. In the middle panel of Fig. 2 is shown two potentials of latencies 2·5 and 3·0 msec. On the ordinate of the graph is plotted the area of each

potential as a percentage of the size of the potential evoked at the beginning of the rise in phrenic activity (0), which was taken as the standard (100 %). It may be seen that although the magnitude of the potentials varied around the 100 % line, there were no consistent, or indeed statistically significant variations from this line.

In the same experiment two potentials of longer latency (25 and 34 msec) illustrated in the bottom panel of Fig. 2 were also evoked. Again, there was no obvious effect on the magnitude of the averaged evoked responses. These results together would indicate that there is no presynaptic modulation of sinus nerve terminals by central respiratory mechanisms, and this is true for both fast and slowly conducting fibres.

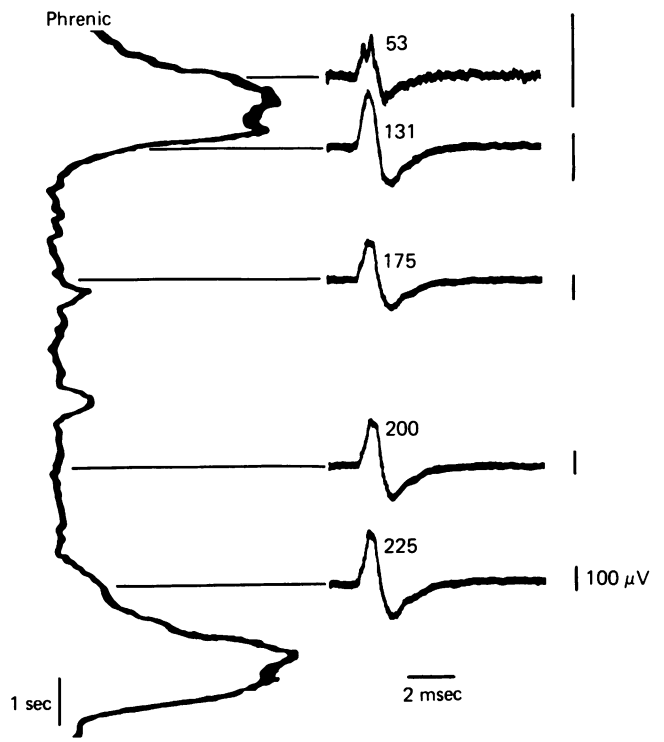


Fig. 3. Cat. Effect of respiration on the excitability of superior laryngeal nerve terminals. Left-hand trace: phrenic nerve activity, rectified and smoothed (inspiration to the right). Right-hand traces: each trace represents the antidromic activity evoked in the superior laryngeal nerve by a stimulus of 20 $\mu$A, 0·1 msec pulses, given at the marked phase of respiration. The figures give the maximum amplitude of each potential in $\mu$V. Each calibration bar represents 100 $\mu$V.

A similar conclusion can be drawn from the experiments on cats in which nine potentials evoked in the sinus nerve (latencies 2–20 msec) were tested in the same manner. Again the averaged responses were never significantly different from the control.

Although the results presented here were consistent, it may be argued that these were simply a reflexion of the inability of the system to detect the excitability changes produced by respiratory cycling. We have repeated the experiments on the

superior laryngeal nerve whose terminals have been shown to be subject to presynaptic modulation (Rudomin, 1967). On the left of Fig. 3 is phrenic nerve activity (rectified and smoothed, inspiration to the right) recorded during a complete respiratory cycle. On the right of the Figure are the antidromically evoked potentials recorded in the superior laryngeal nerve on stimulating within the nucleus of the tractus solitarius. A marked respiratory-related change in the amplitude of the potentials is evident, the potentials being much reduced in size during inspiration.

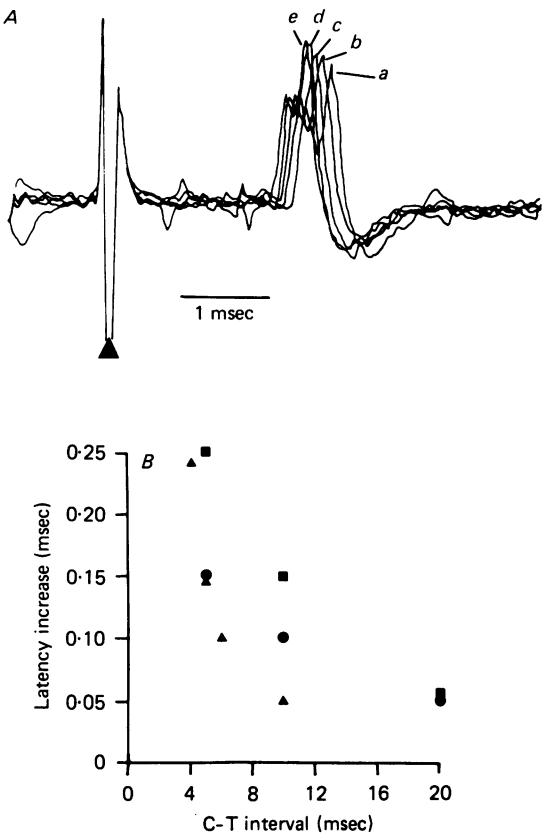


Fig. 4. Cat. The effect of double-pulse stimulation on the excitability of sinus nerve terminals. *A*, the response evoked to the second of two medullary stimuli (0·1 sec pulses, 35 $\mu$A) given at ▲. The Figure superimposes the evoked responses from runs in which the second stimulus follows the first after a period of (*a*) 4 msec, (*b*) 5 msec, (*c*) 6 msec, (*d*) 10 msec. In *e* only one stimulus was applied. *B*, the increase in latency of the evoked response has been plotted against the interval between the two medullary stimuli, for three separate experiments. The symbols (▲) show the results of the experiment illustrated in *A*.

### 3. *Excitability changes produced by stimulation of the sinus nerve terminals*

In the experimental situations described there have been no indications of any procedure eliciting a presynaptic effect on sinus nerve terminals. It is possible, however, that such mechanisms do exist but that they have not been activated by the procedures investigated. If such a mechanism were acting on the nerve terminals,

however, stimulation in the region of the terminals themselves ought to stimulate not only the afferent but also the presynaptic elements. The first of a pair of stimuli to the medulla would then condition the second antidromic response by a direct activation of the presynaptic elements. Two types of response may be expected, either a change in the magnitude of the antidromic response or a change in its latency. In Fig. 4*A* are shown averaged evoked responses in a sinus nerve after conditioning stimuli given to the sinus nerve terminals. As can be seen, the magnitude of the potential decreased while its latency increased, suggesting a hyperpolarization of the terminals. In experiments on cats, seven antidromic potentials in the sinus nerve (latencies 2·5–25 msec) were tested in this way using condition-test intervals of 4–100 msec. In six of the potentials there were increases in the latency of the conditioned response but in only three of these (illustrated in Fig. 4*B*) was the increase statistically significant. The maximum increase in latency was then only 12% and was usually about 6%. The maximum effect was produced with condition-test intervals of 4–10 msec, no effect being noted with intervals greater than 20 msec. Whilst it is possible that a primary afferent hyperpolarization may account for this effect, the short time course of the effect would suggest that it is due merely to the refractoriness of the nerve terminals following the first antidromic response. Latency changes with a similar time course have been described previously for vagal and aortic nerve afferents (Rudomin, 1968).

## DISCUSSION

Presynaptic control of afferent inputs is believed to involve a chemically mediated depolarization or hyperpolarization of the membranes of the afferent terminals. The morphological basis for this action is considered to depend on axo-axonal synapses (Gray, 1962). The polarization changes would be expected to alter the sensitivity, and hence excitability of the terminals to electrical stimulation (Wall, 1958). We have applied this technique to investigate whether the afferent terminals of the sinus nerve in the nucleus of the tractus solitarius are susceptible to presynaptic control during the defence reaction and the respiratory cycle. Our data provides no support for the conclusion that these physiological inputs, which most certainly affect the effectiveness of the baroreceptor reflex, may do so by presynaptic actions on these afferents. According to our results it is unlikely that they are subject to presynaptic modulation under any circumstances.

The absence of such a control during the defence reaction is perhaps the most surprising. Although there has been controversy regarding whether both the vascular and the cardiac components of the baroreceptor reflex can be inhibited by the action of the hypothalamic defence area, the present report, in common with recent observations of others (McAllen, 1976; Coote *et al.* 1979) has confirmed this. Further, McAllen (1976) has shown that stimulation within the hypothalamus, at sites which abolished the sympathetic and cardiac effects of baroreceptor activation, also blocked the baroreceptor input to neurones located in the region of the nucleus of the tractus solitarius which were normally excited by baroreceptor stimulation. Such hypothalamic stimulation in our experiments never gave any indication of presynaptic depolarization of sinus nerve terminals. This negative result was not a function of the technique employed since at the same time hypothalamic stimulation

certainly increased the excitability of other afferents relaying in the glossopharyngeal nerve to the nucleus of the tractus solitarius. Indeed this ability to demonstrate presynaptic effects on glossopharyngeal afferents, which have been suggested indirectly before (Sessle, 1973), might explain the report of Weiss & Crill (1969) that electrical stimulation within the fields of Forel evokes presynaptic inhibition in the terminals of the sinus nerve. They demonstrated presynaptic depolarization with monopolar recording from the sinus nerve, a technique which has been criticized in the past as it records activity from glossopharyngeal fibres rather than sinus nerve activity itself (Lipski *et al.* 1975). In any case, stimulation in the fields of Forel does not abolish the baroreceptor reflex (Wilson, Clarke, Smith & Rushmer, 1961), so their observations are probably analogous to those of the present study in that they had evoked excitability changes in glossopharyngeal afferents, other than those of the sinus nerve.

That presynaptic effects could be demonstrated on afferent fibres relaying to the tractus solitarius might be inferred from the electron microscopic observations of Chiba & Doba (1976). By studying degenerating terminals after transection of nerve rootlets they demonstrated that afferents of the ninth and tenth cranial nerves often formed the post-synaptic element of axo-axonal synapses in the commissural portion of the nucleus, monoamine-containing neurones forming the presynaptic element. This portion of the nucleus is not the major site of termination of baroreceptor afferents though both sinus and aortic nerve afferents do terminate here (Lipski *et al.* 1975; McAllen *et al.* 1979). These observations together might indicate some interaction of sinus nerve and aortic nerve afferents at this level of the nucleus of the tractus solitarius. There is, however, no evidence for a presynaptic interaction between these afferents (Gabriel & Seller, 1970; Jordan & Spyer, 1978*b*). Indeed there is no experimental evidence for aortic nerve afferent terminals showing any excitability changes consistent with presynaptic depolarization or hyperpolarization following stimulation in the nucleus of the tractus solitarius (Rudomin, 1968), an observation we have now confirmed for sinus nerve terminals. In his study, however, Rudomin (1967) demonstrated such effects on superior laryngeal afferents which were amenable to presynaptic modulation from vagal and aortic afferent inputs. In this present study we have shown that the excitability of superior laryngeal afferent terminals varies during the respiratory cycle, in phase with central respiratory activity. Conversely, neither the terminals of the sinus or aortic nerves showed such fluctuations. This observation would indicate that the respiratory 'gating' of baroreceptor and chemoreceptor reflexes, which have often been described (Koepchen *et al.* 1961; Black & Torrance, 1967; Eldridge, 1972; Haymet & McCloskey, 1975) cannot be attributed to a presynaptic mechanism acting on the primary afferent input to the nucleus of the tractus solitarius.

Whilst neuroanatomical and neurophysiological studies are agreed that both sinus nerve and aortic afferents terminate only in the immediate vicinity of the nucleus of the tractus solitarius (see McAllen *et al.* 1979, for discussion), we have obtained no evidence that their terminals are amenable to presynaptic control during two major physiological mechanisms which alter the effectiveness of the reflexes which they mediate. Our evidence from stimulating within the sinus nerve terminals, indicates that our recording techniques were sensitive enough to reveal such changes in glosso-

pharyngeal and superior laryngeal afferents. Alternative mechanisms for these phenomena are discussed elsewhere (Seller & Richter, 1971; Lipski *et al.* 1975; McAllen & Spyer, 1978).

It may however be premature to conclude that no axon terminals occur on these afferents since it is possible that they could make contact on the terminal arborizations at positions distant from the stimulating electrode. This is, however, an unlikely explanation as we routinely made extensive penetrations through the nucleus, but it can only be resolved by intracellular recordings within the afferent terminals. In this context, preliminary observations suggest that the membrane potential of carotid sinus baroreceptor afferents within the nucleus of the tractus solitarius show no fluctuations in phase with central respiratory activity (D. W. Richter, personal communication). Thus on the basis of the present evidence, and the absence of axo-axonal synapses in the intermediate portion of the nucleus of the tractus solitarius (Chiba & Doba, 1975) where carotid sinus baroreceptors mainly project (Lipski *et al.* 1975), we are drawn to the conclusion that baroreceptor afferents (and also chemoreceptor afferents) are uninfluenced by presynaptic mechanisms.

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