While baroreceptor mediated reflex inhibition of vasomotor tone has long been accepted, many workers in the area remain uncommitted about the actual level at which inhibition occurs. Some investigators have indicated that inhibition occurs at supraspinal levels; Lindgren and Uvnas, Scott, Scott and Roberts, while others have reported a spinal level of inhibition; Alexander, and Lim et al.

Beck observed that in the hindquarters of dogs the constrictor response produced by stimulation of the preganglionic lumbar sympathetic trunk (see Beck and Brody for evidence that the upper lumbar sympathetic trunk is predominantly preganglionic) may be increased markedly by section of the sympathetic chain just proximal to the stimulating electrode. This observation led him to postulate that an inhibition must have been present previous to sympathetic chain section, and was removed in part or in whole by the act of severing the chain. Since stimulation was done on the lumbar sympathetic trunk itself, it was concluded that the site at which the inhibitory fibers exerted their action was distal to the stimulating electrode, and was therefore neither in the brain, nor in the spinal cord.

The investigation reported here was undertaken to examine this postulate more fully and, further, to determine whether such inhibitory fibers participate in baroreceptor mediated inhibition of sympathetic activity. Preliminary reports of the present findings have been presented by Beck and Gebber and Beck.

**Methods**

Mongrel dogs, unselected as to sex and weighing from 10 to 20 kg, were anesthetized with 30 mg/kg of sodium pentobarbital, intravenously. All animals were given sodium heparin (5 mg/kg, 100 units/mg) to prevent coagulation of blood. The whole hindquarters, or the individual hindlimbs, were prepared for perfusion with Sigmmotor pumps by a method previously described. The abdominal aorta was exposed via a retroperitoneal approach. The aorta was ligated at the level of L3. A polyethylene cannula attached to rubber tubing leading to the Sigmmotor pump was inserted and tied into the proximal portion of the aorta. A cannula leading from the pump was inserted into the aorta at a point just distal to the point of ligation. When the hindlimbs were perfused separately, the distal cannulae were inserted into the iliac arteries.

The Sigmmotor pump, equipped with a Graham variable speed transmission and vernier scale adjustment, was calibrated over the desired blood flow range. The tension of the pressure plates in the Sigmmotor pump was adjusted to resist a backflow pressure of 300 mm Hg. At any given setting, the delivered volume of blood was remarkably constant. When the blood flow to the extremities is maintained constant, the perfusion pressure gives a continuous record of the peripheral resistance. Unless otherwise stated, the blood flow to the perfused area was maintained constant throughout each experiment.

The mean perfusion pressure to the extremities and the mean systemic blood pressure were monitored on smoked kymograph paper. The perfusion pressure to the hindlimbs was recorded by means of a single arm mercury manometer. The systemic arterial blood pressure was recorded by means of a double arm mercury manometer. Thus to equate the two pressures on the records, the systemic blood pressure must be multiplied by two.

Intravenous injections were made through a cannula inserted into the left external jugular vein. Intra-arterial administration of drugs directly...
into the perfused hindquarters was accomplished by injection into the tubing close to the cannula inserted into the distal portion of the divided aorta.

The sympathetic nerve trunks were exposed for stimulation usually between segments L2 to L4. The sinus nerves were exposed from a ventral aspect after reflection of a portion of the trachea and esophagus. The vagus nerves were exposed in the midcervical area. All stimulations were done by means of American Electronic Laboratory stimulators and bipolar Harvard electrodes. In some experiments, the lumbar rami were ligated and cut or simply crushed with a hemostat. Spinal anesthesia was produced by injecting 1 to 3 cc of 10% procaine into the lumbar canal. In experiments involving neuraxis section, the spinal cord was exposed for section at the atlanto-occipital membrane.

In a number of experiments, pressure on the arterial baroreceptors was varied by bleeding the animal into a reservoir which was part of a blood pressure stabilizer unit. Using this method, as described earlier, the systemic blood pressure could be lowered and maintained at any given level.

In some experiments the neuromuscular blocking agent, decamethonium, was used in a dose of 1 mg/kg intravenously to prevent induced skeletal muscle activity. These animals reacted in the same manner as those which did not receive the neuromuscular blocking agent.

Results

I. EFFECT OF SYMPATHETIC SECTION ON THE RESPONSE TO STIMULATION OF THE LUMBAR SYMPATHETIC CHAIN

Figure 1 illustrates the effect of sympathetic section on the response produced by stimulation of the lumbar chain in a dog which had little spontaneous neurogenic vasoconstrictor tone. In the innervated state, independent stimulation for two minutes of either the left or right lumbar sympathetic caused an initial dilatation. This transient dilatation was succeeded by a constriction which was much more prominent during right sympathetic nerve stimulation. Simultaneous stimulation of both intact sympathetics caused a smaller transient dilatation, but a larger secondary vasoconstriction than did the individual stimulations. Bilateral section of the lumbar chains was performed immediately

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**FIGURE 1**

Effect of sympathetic section on responses produced by efferent lumbar sympathetic nerve stimulation. Upper tracing is the perfusion pressure (PP) to the hindquarters monitored from a single arm mercury manometer; lower tracing is the systemic arterial blood pressure (BP) monitored from a double arm mercury manometer. Base line is common to both tracings. Time intervals are in minutes. N: intravenous injection of 0.5 µg/kg, or intra-arterial injection of 0.3 µg of norepinephrine as indicated; A: intra-arterial injection of either 0.15 µg or 0.3 µg of angiotensin as indicated; S (arrow) both: bilateral stimulation of the lumbar sympathetics; S (arrow) lt: unilateral stimulation of left lumbar sympathetic; S (arrow) rt: unilateral stimulation of right lumbar sympathetics; SYM-X: transection of lumbar sympathetics immediately above the electrode in the same segment.
proximal to the stimulating electrodes which were situated on the L3 (left) and L4 (right) segments. Reflex dilatation produced by the intravenous injection of norepinephrine in the innervated state (panel 1) was abolished after section of the lumbar chains (panel 3), indicating that the peripheral vasoconstrictor pathways had been freed completely from central nervous influence. After bilateral lumbar section, individual or bilateral stimulation of the distal sympathetics failed to produce an initial transient dilatation. The constrictions produced by stimulation of the left chain, and by combined stimulation of both nerves simultaneously were much greater after sympathetic section, but the response to stimulation of the right chain was only slightly increased. It should be noted that the peak level to which the perfusion pressure rose during combined stimulation was also much greater after section of the lumbar chains, the peak level being considerably higher than during stimulation in the innervated state. The vascular constrictions produced by intrarterial injections of angiotensin and norepinephrine were not measurably affected.

Vasoconstriction induced by stimulation of the lumbar chains was regularly increased upon sympathetic section proximal to the stimulating electrodes as shown in table 1. Table 1 shows the mean increase in the response to stimulation of left, right, and both lumbar chains produced by sympathetic section. Responses evoked by sympathetic stimulation were corrected for changes in vascular reactivity as gauged by alterations in the response to intra-arterially injected norepinephrine. The following formula was applied:

\[
\text{corrected sympathetic test} = \left( \frac{\text{observed sympathetic test}}{\text{response after sym-x}} \right) \times \frac{\text{NE constriction before sym-x}}{\text{NE constriction after sym-x}}
\]

**Table 1**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Stimulation of left sympathetic</th>
<th>Stimulation of right sympathetic</th>
<th>Stimulation of both sympathetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar sympathectomy</td>
<td>+37.8 ± 5.37 (21)*</td>
<td>+24.3 ± 6.28 (13)*</td>
<td>+54.4 ± 11.6 (8)*</td>
</tr>
<tr>
<td></td>
<td>( P &lt; .001 )</td>
<td>( P &lt; .01 )</td>
<td>( P &lt; .01 )</td>
</tr>
<tr>
<td>Spinal anesthesia</td>
<td>+12.5 ± 4.91 (14)*</td>
<td>+12.4 ± 8.94 (11)*</td>
<td>+10.4 ± 9.63 (9)*</td>
</tr>
<tr>
<td></td>
<td>( P &lt; .05 )</td>
<td>( P &lt; .2 )</td>
<td>( P &lt; .A )</td>
</tr>
<tr>
<td>Neuraxis section</td>
<td>+27.4 ± 4.64 (10)*</td>
<td>+20.3 ± 7.66 (10)*</td>
<td>+56.9 ± 13.2 (7)*</td>
</tr>
<tr>
<td></td>
<td>( P &lt; .001 )</td>
<td>( P &lt; .05 )</td>
<td>( P &lt; .01 )</td>
</tr>
<tr>
<td>Sinus nerve section</td>
<td>+6.40 ± 2.99 (10)*</td>
<td>+13.0 ± 3.84 (10)*</td>
<td>+14.9 ± 4.95 (10)*</td>
</tr>
<tr>
<td></td>
<td>( P = .05 )</td>
<td>( P &lt; .01 )</td>
<td>( P &lt; .02 )</td>
</tr>
<tr>
<td>Vagus nerve section</td>
<td>+4.60 ± 3.12 (10)*</td>
<td>+0.20 ± 3.06 (10)*</td>
<td>−3.00 ± 5.40 (9)*</td>
</tr>
<tr>
<td></td>
<td>( P &lt; .2 )</td>
<td>( P &gt; .9 )</td>
<td>( P &lt; .5 )</td>
</tr>
<tr>
<td>Hemorrhagic hypotension</td>
<td>+14.8 ± 3.28 (10)*</td>
<td>+20.1 ± 3.75 (10)*</td>
<td>+9.30 ± 5.58 (10)*</td>
</tr>
<tr>
<td></td>
<td>( P &lt; .01 )</td>
<td>( P &lt; .001 )</td>
<td>( P &lt; .2 )</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate number of experiments.
+Change refers to the increase or decrease in the perfusion pressure response caused by the procedure in the left-hand column.
$Statistical analysis was performed using the Student t-test.
In 13 dogs, the effect of lumbar sympathetic section was tested for function of left, as well as right lumbar sympathetics. In the remainder of the 21 experiments, the response was tested only on the left side. The increase, corrected for any change in vascular responsiveness to norepinephrine which occurred following interruption of the sympathetic pathway to the extremities, was statistically significant. The response to stimulation of the left chain was often increased by chain section to a greater extent than stimulation of the right chain. Perhaps this is because the bipolar electrodes placed on the left chain were most often one segment rostral to that placed on the right chain (see table 1).

In animals exhibiting little spontaneous vasoconstrictor tone before section, the perfusion pressure rose during lumbar stimulation to a higher absolute level after section than that reached during the same intensity of sympathetic stimulation in the innervated state. The constrictor response produced by sympathetic stimulation in dogs exhibiting a large amount of spontaneous neurogenic vasoconstrictor tone before section of the sympathetics was also larger after section of the sympathetics. But unlike the response obtained in dogs with little vasoconstrictor tone, the perfusion pressure did not reach a higher level than that obtained upon stimulation before section of the lumbar chains.

II. DISTRIBUTION OF INHIBITORY FIBERS TO PERIPHERAL SYMPATHETIC INNERVATION

The preceding experiments demonstrated that in most animals, inhibitory fibers emerge from the spinal cord above the midlumbar area and course in the sympathetic chain with the preganglionic fibers of the adrenergic system. The observation that there were sometimes considerable differences between dogs in the magnitude of the increase in lumbar sympathetic stimulations following transection of the lumbar sympathetic suggested that the outflow pattern of the inhibitory fibers relative to outflow of the preganglionic adrenergic fibers might vary considerably. Such a difference in outflow pattern could also account for the occasional pronounced difference in the magnitude of the increase in the sympathetic response between two limbs in the same animal as was illustrated in figure 1; and for the observation that less of an increase in the sympathetic response occurred in the extremity in which the electrode was placed more caudally.

To examine whether the inhibitory fibers also emerged from the spinal cord below the level of electrode placement, experiments involving ramisection were done next.

1. Effect of Ramisection on Lumbar Sympathetic Stimulation

In 14 dogs, the effect of progressive section of both the white and gray rami was tested on the constrictor response evoked by efferent stimulation of the lumbar sympathetic chain which had been previously severed in the midlumbar area (L2-L4). Ramisection in the segment immediately below the stimulating electrode resulted in an increased neurogenic response in 9 of 14 dogs. A decrease in the evoked response was seen in 3 dogs and no change occurred in the remaining 2 animals. When ramisection was extended to the lower lumbar and upper sacral segments, the constrictor response evoked by lumbar sympathetic stimulation was almost invariably reduced.

![Figure 2](http://circres.ahajournals.org/) Effect of spinal anesthesia on sympathetic responses evoked by efferent stimulation of the sectioned sympathetic. SPINAL ANESTH: intrathecal injection of 3 cc of 10% procaine at the level of the second lumbar vertebra. Tracings, base line and other symbols as in figure 1.
In the heparinized dog it is very difficult to distinguish white from gray rami so that we could not selectively transect hypothetical inhibitory fibers presumably entering the lumbar sympathetic chain by way of the white rami. Consequently, spinal anesthesia was utilized to determine the proportion of inhibitory fibers normally leaving the cord below the midlumbar electrode placement.

The effect of spinal anesthesia upon the constrictor response evoked by efferent stimulation of the severed lumbar sympathetic is shown in figure 2. Spinal anesthesia was accomplished by injection of 3 cc of 10% procaine into the spinal canal at L2, and its effectiveness was indicated by a marked fall in systemic blood pressure and by respiratory embarrassment. During spinal anesthesia, the constrictor response evoked by unilateral and bilateral sympathetic stimulation was increased out of proportion to the increase in response to intra-arterially injected norepinephrine. Table 1 shows the mean increase in the stimulation response resulting from interruption of inhibitory fibers distributed to the peripheral sympathetic over rami located below the stimulating electrode is usually much less than the loss of inhibition which results from section of the inhibitory fibers which emerge over rami located rostral to the electrode and which pass caudally in the chain beneath the stimulating electrode.

III. ORIGIN OF THE INHIBITORY FIBERS

The chain transection experiments, coupled with the spinal anesthesia experiments, provide evidence that the inhibitory fibers emerge from the spinal cord at various levels and then pass caudal in the sympathetic chain to produce inhibition somewhere in the efferent pathway beyond the point of electrical stimulation of the lumbar sympathetic. Spinal anesthesia does not, however, permit determination of whether the inhibition is spinal or supraspinal in origin. To determine if the inhibition is supraspinal in origin, the effect of transecting the spinal cord in the cervical region upon the lumbar sympathetic responses was next examined.

1. Effect of Cervical Spinal Cord Transection on Lumbar Sympathetic Stimulation

Transection of the spinal cord at C1 regularly increased the constrictor response to stimulation of the intact lumbar sympathetic chain in 10 dogs (see table 1 for data). When transection of the neuraxis produced a small or moderate fall in perfusion pressure (indicating a small amount of vasoconstrictor neurogenic tone existing before transection) the level reached by the perfusion pressure during sympathetic stimulation after neuraxis section, usually rose above that reached before transection of the spinal cord. Such an experiment is illustrated in figure 3. The rise in perfusion pressure produced by stimulation of the left intact sympathetic chain was enhanced markedly after neuraxis section at C1. As is shown also in this figure, spinal cord section had little effect on the response to stimulation of the previously sectioned right lumbar chain. In two other experiments, spinal cord section increased the response to stimulation of the previously severed sympathetic, but not to the same degree as was observed for the intact chain.

From this type of experiment, it can be concluded that the peripherally distributed inhibitory fibers take origin in large part from cell bodies located at supraspinal levels.

To determine if the inhibition was initiated over the classic pressoreceptor pathways, experiments were next performed involving sinus nerve section, vagotomy, lowering and raising systemic arterial blood pressure, afferent sinus and vagal stimulation, and finally, painting of the carotid sinus with norepinephrine.

In all of these experiments, the lumbar sympathetic was first divided rostral to the stimulating electrode to avoid complications in interpretation brought about by what might otherwise be induced changes in vasomotor tone of central origin. After interruption of the efferent sympathetic pathway by
REFLEX INHIBITION OF VASOCONSTRICTOR ACTIVITY

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FIGURE 3

Differential effect of spinal cord transection on neurogenic responses evoked from the intact left lumbar sympathetic and the previously sectioned right lumbar sympathetic in a dog with independently perfused hindlimbs. Left sympathetic chain intact; right sympathetic chain sectioned immediately rostral to electrode. Abbreviations It and rt shown at right of record designate the perfusion pressures to the left and right extremities, respectively. C₁ SEC: transection of spinal cord at the level of the first cervical vertebra; cps: frequency of stimulation in cycles/sec. Otherwise tracings, base line and symbols as in figure 1.

normal chain section, any change in the response to electrical stimulation of the efferent sympathetic chain can be influenced only by fibers distributed to the sympathetic chain over rami located below the level of sympathetic stimulation. While section of the chains immediately above the stimulating electrode removes the possibility of fluctuations in perfusion pressure brought about by central autonomic modulation of the adrenergic system, it unfortunately eliminates also a large portion of the inhibitory pathway distributed to the peripheral sympathetic. The results shown in the following sections are therefore much less than would be anticipated had the lumbar sympathetic chains been left intact. Elimination of reflex dilatation in the perfused area, normally produced by the intravenous injection of norepinephrine, was taken as evidence for the interruption of the adrenergic pathway to the extremities. If the first bilateral transection of the lumbar sympathetics failed to eliminate the reflex, the sympathetics were transected at progressively lower levels until the reflex disappeared. In many experiments the disappearance of reflex constriction normally produced by short term asphyxia was also used as a test for complete interruption of the adrenergic pathways to the extremity.

2. Effect of Sinus Nerve Section and Vagotomy on Lumbar Sympathetic Stimulation

Figure 4 illustrates the effect of bilateral section of the sinus and vagus nerves on the constrictor response evoked by stimulation of the distal ends of the cut lumbar sympathetic chains. Section of the sympathetics was performed at L3. Control responses evoked by stimulation of the left and right sympathetic chains, as well as by bilateral stimulation, are shown in the initial portion of the record. Bilateral section of the sinus nerves greatly enhanced the constrictor responses evoked by sympathetic stimulation. Figure 4 shows that the responses evoked by bilateral sympathetic stimulation were very reproducible both before and after sinusectomy. The dramatic enhancement in neurogenically evoked constriction occurred without apparent change in the vascular response induced by the intra-arterial injection of norepinephrine. Bilateral vagotomy produced a further increase in the response evoked by stimulation of the left but not by the right, lumbar chain. The effects of sinus nerve section and vagotomy are summarized in table 1. Bilateral sinus nerve section caused significant increases in the constrictor responses evoked by sympathetic stimulation, but vagotomy did not.

3. Alterations in Systemic Blood Pressure

The effect of acutely lowering and subsequently elevating systemic blood pressure on the response to efferent lumbar sympathetic stimulation, is illustrated in figure 5. Electrodes were placed on the sectioned sympathetic trunks between L2 and L3. After control stimulations were performed (panel 1), the
animal was bled from the side arm of a T-tube inserted in the proximal aorta into a reservoir which was part of a constant pressure system (see Methods). The animal was bled to a systemic blood pressure of 74 mm Hg and was subsequently stabilized at this level. During the period of low blood pressure stabilization the perfusion pressure to the hindquarters rose considerably above the level existing before hemorrhage. Since the adrenergic pathways to the extremities had already been interrupted by lumbar sym-

![Graph](image-url)

**FIGURE 4**

Effect of bilateral section of the sinus nerves (BILAT SINUS-X) and bilateral vagotomy (BILAT VAGOT-X) on neurogenic responses evoked from the previously sectioned lumbar sympathetic chains. Tracings, base line and symbols as in figure 1.

![Graph](image-url)

**FIGURE 5**

Effect of blood loss and retransfusion on neurogenic responses evoked from the previously sectioned lumbar sympathetics. See figure 1 and text for details.
pathetic section, the increase in the perfusion pressure must have been due to an increase in circulating constrictor agents. The responses to individual and bilateral sympathetic stimulation were increased during the hypotension. In contrast, the constrictor response produced by the intra-arterial injection of norepinephrine remained nearly the same, (panel 2). Re-infusion of the withdrawn blood elevated the systemic blood pressure almost to the level observed in the control period. There was probably a concomitant decrease in circulating humoral constrictor substance resulting in a return of the perfusion pressure towards normal. The increase in systemic blood pressure was associated with a return of the sympathetic responses toward control magnitude (panel 3). Conversely, the vascular response produced by the intra-arterial injection of norepinephrine was increased upon return of the withdrawn blood. The results obtained in 10 such experiments are shown in table 1.

4. Effect of Carotid Sinus and Afferent Vagal Nerve Stimulation on Lumbar Sympathetic Stimulation

The effect of carotid sinus nerve stimulation on the response to electrical activation of the distal ends of the severed lumbar sympathetic trunks was tested in a series of six animals. Figure 6 illustrates two of these dogs. In panel 1 of figure 6A, the intravenous injection of norepinephrine produced a reflex fall in pressure of the innervated perfused hindquarters. Bilateral section of the sympathetics was then performed at L3. The subsequent intravenous administration of norepinephrine produced no reflex effects in the hindquarters showing that the vasoconstrictor pathways to the hindquarters had been interrupted (panel 2). The sinus nerves and vagi were next sectioned. After that the severed lumbar sympathetics were stimulated at 1 cycle/sec to restore the tone existing before sympathetic section. Stimulation of the central end of the sinus nerve, during sympathetic stimulation, produced a dilatation in the perfused extremities and a simultaneous reduction in systemic blood pressure (panel 3). The sympathetics were then stimulated at a higher frequency (6 cycles/sec) and stimulation of the sinus nerve was repeated. A greater fall in perfusion pressure occurred.

Figure 6B illustrates a similar experiment with one added feature. When the central end of the sinus nerve was stimulated during efferent lumbar sympathetic stimulation, two components of dilatation were observed in the perfused hindquarters. An immediate fall in perfusion pressure (shown by the white brackets), which occurred simultaneously with the systemic depressor response, was followed by a secondary delayed fall in perfusion which occurred after sinus nerve stimulation had been stopped. The onset of the secondary dilatation corresponded with the delay time of the perfusion circuit; that is, to the time required for a substance liberated into the blood stream to pass through the pump circuit to reach the perfused limbs. When sympathetic nerve stimulation was stopped and sinus nerve stimulation repeated, stimulation of the sinus nerve no longer produced an immediate fall in perfusion pressure (white brackets); but the secondary delayed fall was even greater than during sympathetic stimulation. The remaining four animals in this series conformed to either one or the other pattern illustrated in figure 6A and B.

Figure 7A shows that it is also possible to reduce by vagal stimulation the sympathetic tone induced in the extremity by efferent lumbar sympathetic nerve stimulation. The sympathetic chains had been sectioned earlier. Proof that the extremity had been previously decentralized is provided by the absence of a reflex dilatation in the extremity when norepinephrine was injected intravenously. Sympathetic tone, induced by stimulating the lumbar chains (2 cycles/sec, 4 v, 5 msec) was reduced when the afferent vagus was stimulated at 3 v, 7 msec and 20 to 40 cycles/sec. Injection of norepinephrine, during the replacement of sympathetic tone, produced almost no reflex inhibition of the restored tone in this debuffered preparation. Stimulation of the vagi in the absence of replacement of sympathetic tone did not produce a dilatation in the denervated extremity.
As shown in figure 7B, topical application of norepinephrine (1:1000) to the intact carotid sinus area, also depressed the constrictor response evoked by stimulation of the distal ends of the cut lumbar sympathetic chains (two dogs). The constrictor response evoked by the intra-arterial injection of norepinephrine was unaltered. As expected, a systemic depressor response was produced by the topical administration of norepinephrine to the sinuses.

Discussion

A. TONIC INHIBITION OF SYMPATHETIC TONE OCCURRING AT A SITE PERIPHERAL TO THE SPINAL CORD

Sympathetic section, ramisection or spinal anesthesia increases significantly, the constrictor responses produced by efferent stimulation of the lumbar sympathetic chain at a predominantly preganglionic level. While these results are compatible with the postulate presented previously, Beck,⁶ that inhibitory fibers emerge from the spinal cord to inhibit

![Figure 6](http://circres.ahajournals.org/)

Peripheral inhibition of sympathetic tone by afferent sinus nerve stimulation. Dogs in both A and B of the figure had splanchnic nerves sectioned bilaterally just above the diaphragm 24 hours previous to the experiment. BILAT SYMP-X: bilateral transection of lumbar sympathetic chains; BILAT SINUS-X and VAGOT-X: bilateral section of the sinus and vagus nerves; SYMP: bilateral efferent stimulation of lumbar sympathetics; RS: stimulation of right sinus nerve. In part A of figure the blood pressure and perfusion pressure co-ordinates were simultaneous; in part B of the figure, the perfusion pressure tracing is 30 seconds out of phase with the blood pressure tracing. Tracings, base line and other symbols are the same as in figure 1. See text for explanation of white bars and other details.
REFLEX INHIBITION OF VASOCONSTRICTOR ACTIVITY

adrenergic discharge, other alternative explanations must be ruled out for this postulate to become entirely acceptable.

It could be reasonably supposed that the greater response to sympathetic stimulation following sympathetic section is an artifact to be anticipated when spontaneous discharge of norepinephrine from the intact sympathetic is arrested by nerve section. A log-dose response to neurogenically released norepinephrine would be expected to be similar to that seen when increasing doses of norepinephrine were injected intra-arterially to the perfused limb. Thus, the release of a fixed amount of norepinephrine from the sympathetic nerve at a time when spontaneous discharge is occurring would be expected to produce less vascular constriction than would the same amount of norepinephrine released in the absence of spontaneous sympathetic discharge following interruption of the sympathetic pathway. While this explanation could account for an exaggerated neurogenic response following sympathetic section in dogs having considerable vasoconstrictor tone in the innervated state, it cannot account for the much greater increase in the neurogenic response following section of the lumbar chains in dogs with little or no vasoconstrictor tone previous to section. This was exemplified in figure 1 where chain section resulted in an increase in the sympathetic stimulation response which was ninefold greater than the decrease in the perfusion pressure produced by chain section. Indeed, the constrictor response produced by stimulation rose after chain section to a level 48 mm Hg above the peak response obtained before chain section. This cannot be explained by an alteration in the log-dose response curve resulting from the absence of neurogenic secretion following interruption of the adrenergic pathways.

In the experiments dealing with spinal anesthesia, the increase in the neurogenic constriction response which occurred following anesthesia cannot possibly be explained by a change in the log-dose response curve due to removal of existing neurogenic tone. The vasoconstrictor fibers distributed to the periphery through the portion of the sympathetic chain located beneath the stimulating electrode had been purposely interrupted before spinal anesthesia. The effect of spinal anesthesia was then tested upon control constrictor responses induced in the extremity by efferent stimulation after the chain had been severed. The enhanced sympathetic responses which occurred following either sympathetic section

FIGURE 7

A: Peripheral inhibition of sympathetic tone by afferent vagal nerve stimulation. SYMP-bilateral efferent stimulation of lumbar sympathetics; V: afferent vagal nerve stimulation; cps: frequency of sympathetic or vagal nerve stimulation in cycles/sec. White dots in left panel show beginning of vagal stimulation; white bars in right panel show the duration of vagal stimulation. Black bar below left panel shows duration of sympathetic stimulation. Splanchnicectomy was performed as in figure 6. B: Effect of the topical application of norepinephrine to the carotid sinuses on peripherally induced sympathetic tone. TOPICAL NOREPI: topical application of norepinephrine to sinuses between portions of record shown in figure 7B. White dots show beginning of electrical stimulation of sympathetics. Otherwise, tracings, base line and symbols are the same as in figure 1.

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proximal to the electrode, spinal anesthesia, or ramisection could theoretically be attributed to acute sensitization of the hindlimb vasculature to released catecholamine. Such a possible explanation for the increased response seems to be eliminated by two observations. First, the response of the hindlimb vasculature to intra-arterial norepinephrine, which is generally accepted as being the neurohumour released from sympathetic nerves, was, on the average, little changed from control after nerve section. When increases in the response to norepinephrine were seen, the neurogenic response was adjusted correspondingly for the increased vascular responsiveness. Even after adjustment for changes of reactivity, the neurogenic response was increased significantly over control.

The second point, which excludes sensitization of the vasculature as a mechanism responsible for the increase in the sympathetic vasoconstrictor response, is that in the case of the spinal anesthesia experiments, the blood pressure stabilization experiments, and the experiments dealing with sinus and vagus nerve section or stimulation, the adrenergic pathway emanating from the medulla to the extremity had already been interrupted by lumbar sympathetic nerve section proximal to the stimulating electrode before testing for inhibition. After lumbar nerve section, time was allowed for the neurogenic vasoconstrictor response produced by chain stimulation, to become constant. Since the response was constant, it follows that any sensitization which might be hypothesized to develop rapidly after nerve section, would necessarily have become maximal before the test for inhibition in the above experiments. This is not meant to deny the well known sensitization which requires several days to reach a maximum, but the slowly developing sensitization would be so minor in the relatively short period required to conduct the test for inhibition that it could not contribute materially to the observed increase in the neurogenic constriction following spinal anesthesia, sinusectomy or low blood pressure stabilization.

From these observations it is concluded first, that the greater neurogenic constrictor response, seen after procedures which interrupt efferent autonomic pathways, results from the loss of an inhibition present before interruption of the nerve pathways, and second, that the site at which the inhibitor is neurogenically released is distal to the stimulating electrode in the efferent pathways of the sympathetic.

B. DISTRIBUTION OF INHIBITORY FIBERS

It has been pointed out that the response to lumbar sympathetic stimulation can be increased by section of the sympathetic chain proximal to the stimulating electrode, and that a further increase in response can be accomplished in most animals by subsequently performing spinal anesthesia or ramisection. Since our electrode placement remains constant throughout the experiment, this indicates that the inhibitory fibers which reduce the effectiveness of stimulation of the adrenergic system emerge from the spinal cord over rami situated both above and below the original point of nerve section. This is equivalent to stating that some of the inhibitory fibers emerge from the spinal cord below the level of emergence of the corresponding sympathetic fibers whose effective discharge the inhibitory fibers suppress, while the remaining inhibitory fibers leave the cord at a higher level, probably in conjunction with preganglionic sympathetic fibers.

The considerable variation noted in the degree of inhibition on left and right chains, and in the differences in the amount of inhibition from dog to dog suggests that the pattern of inhibitory fibers may well vary from dog to dog. Undoubtedly, however, a considerable amount of the variation can be explained on the basis of differences in electrode placement and the amount of tonic inhibitory discharge in different dogs. However, the important point of these experiments is not whether the outflow pattern of inhibitory fibers varies considerably from dog to dog; but, rather the demonstration that the relative levels of emergence of the inhibitory fibers and preganglionic fibers of the adrenergic...
system are often considerably different. This finding is illustrated diagrammatically in figure 8, where some of the inhibitory fibers are shown emerging below sympathetic fibers which they inhibit. Other inhibitory fibers emerge along with, or perhaps above, the corresponding level of outflow of preganglionic sympathetic fibers.

The evidence is very compelling that at least some inhibitory fibers emerge from the cord and course caudad in the lumbar sympathetic with the adrenergic preganglionic. It is logical then, to ask why the inhibition, lost upon sympathetic section, is not restored by the same stimulus which excites the adrenergic system? A plausible explanation is that the low frequency required to provoke marked adrenergic discharge is inadequate to produce a significant release of the inhibitory substance from inhibitory efferents lying beneath the stimulating electrode. Such a hypothesis is in accord with the known fact that the Renshaw inhibitory cells normally discharge at very high frequencies, whereas in our experiments, the inhibitory fibers would be stimulated at only 1 to 2 cycles/sec after decentralization.

C. CENTRAL REFLEX CONTROL OF PERIPHERAL INHIBITION

1. Supraspinal Origin of Peripheral Inhibition

A question which arises from the foregoing discussion is whether the inhibition emanates from a tonically discharging center in the brain or spinal cord or whether the inhibition is initiated in the innervated state by activation of inhibitory afferents lying beneath the stimulating electrode. If the latter were the case, stimulation of the central end of the severed nerve should restore any inhibition which reached the extremity over the inhibitory fibers leaving the cord below the point of chain section. To test this hypothesis, several experiments were done in which two sets of bipolar electrodes were placed upon the same intact sympathetic segment. It was then established that stimulation at the same parameters through either electrode produced the same sympathetic response in the innervated state. The nerve was subsequently sectioned between the two electrodes and the stimulations repeated. Stimulation through the lower electrode resulted in the typically increased response characteristically observed after sympathetic section and discussed in the foregoing section. Stimulation

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**FIGURE 8**

Diagram of peripheral distribution of inhibitory fibers. A preganglionic neuron (E) and a postganglionic neuron (C) of the sympathetic system are shown in solid black lines. Inhibitory fibers are represented by broken lines. Some inhibitory fibers emerge over same rami as corresponding preganglionic neurons of sympathetic system and some emerge over rami below corresponding sympathetic outflow. See text for further explanation.
through the upper electrode alone, evoked neither a constriction nor a dilatation in the ipsilaterally perfused extremity irrespective of the parameters of stimulation employed. Simultaneous stimulation through both electrodes failed to reduce the sympathetic response to the presection level irrespective of whether the proximal stimulation was carried out at the same frequency or at a much higher frequency (1 to 300 cycles/sec) than in the control states. These observations, coupled with the finding that spinal anesthesia and cervical cord section augmented the constrictor response evoked by sympathetic stimulation in previously decentralized dogs, leave little alternative but to accept that the inhibition emanates, at least in part, from a tonically discharging area in the brain.

2. Baroreceptor Influence on Peripheral Inhibition

Since the foregoing results indicate that at least a portion of the tonic inhibition of sympathetic vasoconstrictor tone to the hind-limb of the dog occurs at a site peripheral to the central nervous system, the next step in the investigation was to establish whether a relationship existed between the classic baroreceptor reflexes and the activity of the peripheral inhibitory system.

It is difficult to test for peripheral inhibition of baroreceptor origin. This is because the loss in spontaneous adrenergic tone, resulting from central inhibition, cannot normally be distinguished from that lost by peripheral inhibition when the vasomotor pathways are left intact. To make such a distinction it is necessary first to interrupt efferent adrenergic pathways from the vasomotor center and then to induce adrenergic tone by electrical stimulation at a more peripheral point such as the lumbar sympathetic. Providing that such a procedure does not also interrupt the inhibitory pathway, it is then possible to evaluate the baroreceptor influences on the peripherally induced adrenergic tone. It has already been demonstrated that a portion of the inhibitory outflow alluded to above, remains intact in most animals after lumbar chain section so that a qualitative, if not a quantitative, test for inhibition is possible.

Utilizing such a test for baroreceptor induced inhibition, it has been shown that section of the sinus nerve resulted in a significant increase in the response to lumbar sympathetic stimulation. The converse procedure of electrically stimulating the previously sectioned carotid sinus nerve restored the inhibition which was lost by sinus nerve section. Stimulation of the physiological inhibitory receptor by painting the sinus area with norepinephrine also reduced the response to efferent lumbar sympathetic nerve stimulation.

These results suggest that the peripheral inhibition originates in part from the classic buffer zones innervated by the sinus nerves. That the receptors initiating the inhibition are pressoreceptive, is indicated by the experiments involving hypotension and return of withdrawn blood. Decreasing blood pressure, which would lessen tension upon stretch receptors, decreased the inhibition. Return of the withdrawn blood, which would restore the tension upon stretch receptors, restored the inhibition.

For an unexplained reason, vagotomy failed to produce a significant change in the constrictor response elicited by lumbar sympathetic stimulation. In addition, stimulation of the central end of the cut vagi produced less consistent inhibition of electrically induced sympathetic tone than did sinus nerve stimulation. Since the compound vagal trunk was used in these experiments, it is possible that vagal afferents with a function antagonistic to those of the aortic depressor nerve play a vasoregulatory role. If so, the expected effect of aortic depressor nerve denervation or activation may have been masked by some factor as yet unexplored.

A secondary delayed dilatation which was often observed in the perfused area upon sinus nerve stimulation deserves special mention. This delayed dilatation, which is illustrated in figure 6B, occurred both in the presence and in the absence of stimulation of the sectioned sympathetic. The delay period required for the dilatation to appear in the perfused area was equal in time to the delay.
period required for a dilator substance to pass through the perfusion circuit, and this time, could be varied by altering the speed of the perfusion pump. The delayed hindlimb dilatation is therefore of humoral rather than neurogenic origin.

Theoretically, the delayed dilatation could result from the inhibition of secretion of circulating adrenergic amines, or alternatively, the dilatation could reflect the inhibition into the circulation of a dilator substance when the sinus nerves are stimulated. Because the response occurred just as frequently in dogs in which the splanchnic nerves were removed bilaterally we favor the latter view. A similar dilatation was observed in the denervated perfused cat limb by Khaiutin. Bacq et al. reported that sinus nerve stimulation produces a fall in blood pressure after total removal of the sympathetic chains in the cat. The possible significance of these observations undoubtedly deserves further investigations.

It is not the intention of the authors to propose that the peripheral inhibitory system is distributed to all vascular beds, or to deny the existence of a central component of inhibition of vasoconstrictor tone. Very sound evidence exists to show that inhibition of vasoconstrictor tone can occur at sites located in the central nervous system (Adrian et al., Beck and Dontas, Bronk et al., Dontas, and Iggo and Vogt). Such results suggest that adrenergic discharge can also be inhibited, at least in part, at a spinal or supraspinal level. But until experiments of the type quoted in the above articles have been done for the hindquarters and elsewhere, we should not assume as a proven fact that all portions of the sympathetic system are necessarily inhibited at a central locus.

The results presented show clearly that inhibition of supraspinal origin occurs at an extraspinal locus, but unfortunately they do not permit defining the exact locus from which the inhibitor is released. Theoretically, the inhibitor could be released at any one of a number of ganglionic sites, e.g., presynaptic cholinergic terminals, postsynaptic dendrites, cell soma or axon hillock. The inhibition might also occur at more peripheral ramifications of the adrenergic neuron. Localization of the exact site will probably have to await application of classic neurophysiological techniques.

Summary

Section of the lumbar sympathetic chain just proximal to a stimulating electrode most often results in a large increase in the neurogenic constrictor response to stimulation. The increase could not be accounted for by removal of sympathetic discharge present before section, or by an increase in vascular sensitivity to either exogenous or neurogenically released adrenergic amine. The increased neurogenic constriction is attributed to the removal of an inhibition present before nerve section. The inhibitory fibers are distributed over the classic sympathetic outflow and take origin at least in part at a supraspinal level. The inhibition is lost or markedly reduced by hypotension, spinal cord section, spinal anesthesia, section of the preganglionic sympathetic, or by section of the sinus and vagus nerves. The inhibition, lost by sinus and vagus nerve section or by induction of hypotension, can be restored by stimulation of the central ends of the cut nerves and by replacement of blood, respectively. It is concluded that the conventional pressoreceptor reflexes act to inhibit vasoconstrictor tone, at least in part, at a site in the vasoconstrictor pathway peripheral to the spinal cord.

References

Reflex Inhibition of Sympathetic Vasoconstrictor Activity at a Peripheral Locus
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