CENTRAL NERVOUS CONTROL OF VENOUS TONE—I:

EFFECT OF SYMPATHETIC CHAIN STIMULATION ON CUTANEOUS CAPACITANCE AND RESISTANCE VESSELS

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Summary: Effects of sympathetic chain stimulation on small capacitace and resistance vessels of skin were observed in the dog with the "occluded hind limb" technique. At lower frequencies of stimulation (1-8/sec) the pressure rises were of similar magnitude in both types of vessels. At higher frequencies the capacitance vessel response achieved its maximum (37 ± 1.7 *mmHg*) earlier *i.e.* at 12-16/sec, than the maximum of 67.5 ± 2.7 *mmHg* in the resistance vessel response i.e. at 20-24/sec. The rate of pressure fall after sympathetic stimulation was slower in the capacitance vessel than the resistance vessel. These responses represented active constrictions of respective vessel wall and were not accompanied by the increase of systemetic arterial pressure. The capacitance vessel response was not affected by the duration of circulatory arrest upto 9 minutes but the resistance vessel response showed a progressive decrease with the increase in the duration of circulatory arrest.

Both capacitance and resistance vessels of the skin possess alpha adrenergic receptors which are engaged by norepinephrine released at the sympathetic nerve endings. Receptors on both types of vessels were equally blocked by phenoxybenzamine. Blocking of the sympathetic chain stimulation response with phenoxybenzamine (tested upto a dose level of 15 *mg/kg*) was never complete although i.v. norepinehrine induced systemic arterial pressure increase was always completely blocked. Resistance and capacitance vessel responses induced by the neurotransmiter released at the sympathetic nerve endings did not engage the beta adrenergic receptors.

Key words: capacitance vessel resistance vessel adrenergic receptors adrenergic receptor blocking agents phenoxybenzamine propranolol sympathetic chain neurotransmitter cutaneous circulation

INTRODUCTION

Activation of sympathetic fibres produces constriction of the cutaneous vessels (5, 6, 15, 16). Magnitude of the constrictor response is proportional to the rate of sympathetic discharge which can be simulated experimentally by electrical stimulation of sympathetic chain with graded stimulus frequencies. Mellander (20) observed that the frequency-response curve of the vein has characteristics which are different from those of the arterial curve. It has been also reported that veins and arteries do not much differ in their respective responsiveness when sympathetic chain is stimulated at different frequencies (4). Both alpha and beta adrenergic receptors have been suggested to be present on the veins. The alpha receptors are constrictor in nature (3, 8, 10, 18, 29). With regard to beta receptors both constrictor (9, 14) and dilator (1, 28) actions have been reported.

In this paper we report the distinctive effects on cutaneous veins and arteries obtained on stimulation of sympathetic chain at different frequencies. The use of adrenergic receptor blocking agents, in addition, has permitted the elucidation of the role of alpha and beta receptors in the neurogenically induced responses of skin vessels.

MATERIALS AND METHODS

Twenty one mongrel dogs of either sex weighing between 8-14 *kg* were anaesthetized with alpha chloralose (80 *mg/kg* intravenously). The anaesthetic was supplemented at 10-15 *mg/kg* whenever required to maintain the same approximate level of anaesthesia.

Stimulation of sympathetic chain: The abdomen was opened with a midline incision to expose the right sympathetic chain at lumbar level. The intestines were retracted and covered with gauze packs socked in warm saline (38° - 39°C). Connective tissue sheath covering the sympathetic chain at lumbar 4 and 5 was gently removed with a glass seeker after a careful knife cut. Its peripheral end was mounted on a bipolar silver electrode which was connected to an S4 Grass stimulator through a stimulus isolation unit. Spread of the current to the surrounding tissue was prevented by the polythene shielding of the silver electrodes and connecting wires, and by surrounding the electrodes with cotton swabs soaked in liquid paraffin. Incision was stitched back at the end of dissection.

Capacitance and resistance vessel tone: Changes in the tone of capacitance and resistance vessels of the cutaneous vascular bed were measured by the occluded limb technique earlier employed by Wallace (26). The authenticity of the technique has since been reported by a number of authors (19, 25, 30). Broad principle of this technique is the temporary isolation of the vascular bed of a limb so that the volume of vessels remains fairly constant. Change in the pressure of the vessels at isovolumetric stage is considered to reflect the change in their respective calibre. This was achieved in this study by inflating a 3'' wide pressure cuff wrapped round the limb above the knee joint to a pressure of 280-300 *mmHg*. The cuff was secured in place by applying a plaster of paris bandage over it.

Venous pressure was measured through a polythene catheter introduced into a second order tributary of the saphenous vein at the ankle level. Poterior tibial artery was catheterized just above the ankle to simultaneously record the resistance vessel pressure of the same vascular bed. These catheters were connected to the Statham strain gauge pressure transducers model P23BC. Output of these transducers was fed into low level DC pre-amplifiers to be recorded on a Grass model 5*P* ink-writing polygraph.

While recording pressures with this technique it was observed that the capacitance vessels were resistant to local metabolic changes associated with circulatory arrest but the resistance vessels were not as also observed earlier (17). In order to assess the effect of circulatory arrest on the responsiveness of skin vessels, the sympathetic chain was stimulated at successive intervals after occluding the limb in 7 dogs. Pooled data showed that after 4 min of circulatory

arrest the resistance vessel response became 78.6±1.56% of the maximum as obtained immediately after the circulatory arrest. After 5 and 9 min it was 74.2±2.74% and 62.01±4.85% of the maximum respectively. The venous pressure response did not exhibit any significant decrement even after 9-10 minutes of circulatory arrest (Fig. 1). Therefore, while analysing the data, either those responses which were obtained within 3-4 min of circulatory arrest were included or appropriate corrections in the responses of the resistance vessel were made as required by the data depicted in Fig. 1.

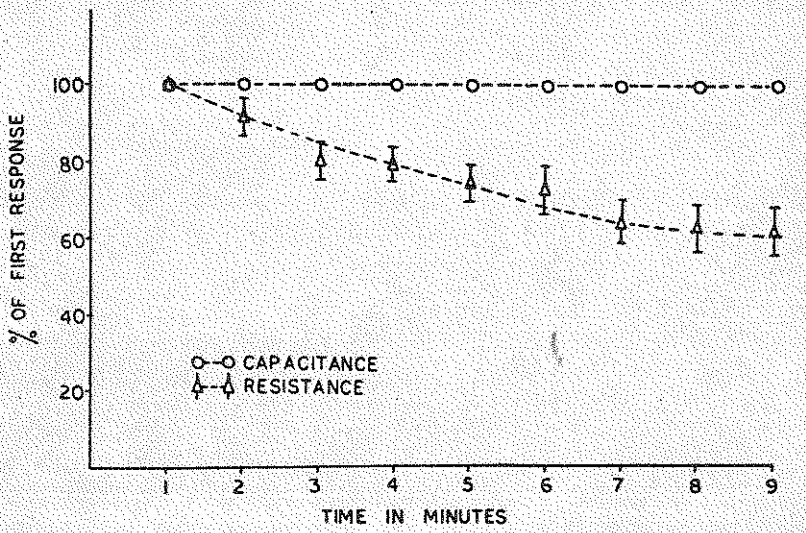

Fig. 1: Data of the effects of sympathetic chain stimulation at successive intervals during the circulatory arrest of hind limb obtained from 7 dogs, was collated together and statistically analysed. The result is plotted in terms of the percentages of the first response i.e. during Ist min of circulatory arrest.

Other parameters: Systemic arterial pressure was recorded from the left femoral artery with the help of a Statham P23AC transducer. Respiration was recorded by measuring the chest movements pneumographically with the help of a Statham PT5A volumetric pressure transducer.

Administration of drugs: Noradrenaline (nordin-Unichem) at graded doses of 0.25, 0.5 and 1.0 $\mu g/kg$ and Isoprenaline (isoprenaline sulphate-Unichem) 1-2 $\mu g/kg$ was administered to excite alpha and beta adrenergic receptors. Phenoxybenzamine (Dibenzyline S.K.F.) at various dosages was given to block the alpha adrenergic receptors. Propranolol (Inderal I.C.I.) Was used to block the beta adrenergic receptors. In some animals flaxedil (gallamine triethiodide) at 3 mg/kg was injected to paralyse the animal so that respiratory effects on the venous pressure response are obviated. All injections were made through a cannula kept *in situ* in the cephalic vein of the right forelimb.

Miscellaneous: Trachea was connulated in all animals as a routine. Artificial respiration was instituted through the tracheal cannula from a positive pressure respiratory pump whenever the

animal was paralysed with flaxedil. Rectal temperature was monitored throughout the experiment in all animals. Body temperature was maintained at 37°C to 38°C with heating pads.

RESULTS

Basal pressures on circulatory arrest: Occluding the limb by raising the cuff pressure to 280-300 *mm*Hg produced an immediate rise followed by a falll in the saphenous vein pressure and a fall in the posterior tibial artery pressure. Within 1-2 min these pressures were in equilibrium and stood between 10-30 *mm*Hg and 5-10 *mm*Hg respectively. Variation of basal pressure within these ranges did not produce any significant variation in the responses induced by stimulation of sympathetic chain.

Sympathetic chain stimulation: Stimulation of sympathetic chain always produced an increase in the occluded limb vein and arterial pressure. In both cases the rise in pressure occurred quickly within 3-5 sec of the onset of stimulation and was maintained throughout the period of stimulation (40-60 sec). The rate of fall in the vein pressure on cessation of stimulation, however, was much slower than that in the occluded limb arterial pressure (Fig. 2). For example 10 seconds after stimulation, the resistance vessel recovered 79.01±1.27% while the capacitance vessel recovered only 24.35±1.03%. This difference assessed at various time intervals after the stimulation was statistically significant.

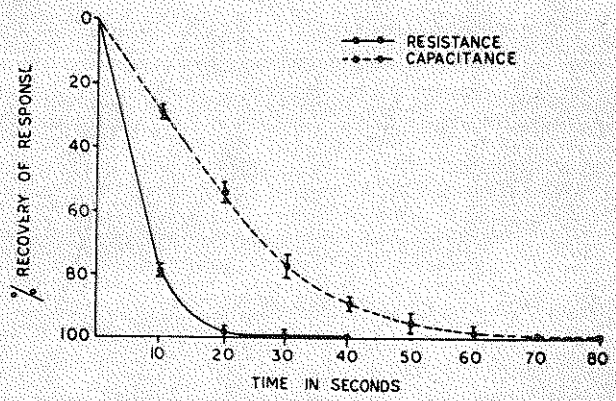

Fig. 2: Curves depicting the respective recovery phase of resistance and capacitance vessels after sympathetic chain stimulation. Each point represents the mean of twelve observations.

When a supramaximal strength of stimulus was delivered at different freuqencies, the response of both the capacitance and the resistance vessel was proportional to the frequency of stimulation (Fig. 3a). At lower frequencies the pressure increase in both types of vessels was almost equal but at higher frequencies the pressure increase in the resistance vessel was more than that in the capacitance vessel (Table I). The maximum of the capacitance vessel *i.e.* 37.08±1.7 *mm*Hg was achieved with a freuqncy range of 12-16/sec, and that of the resistance vessel *i.e.* 67.5±2.7

TABLE I*: Effect of ipsilateral sympathetic chain stimulation.

	*Increase in pressure (mmHg) on stimulation** of sympathetic chain*						
	1/sec	*2/sec*	*4/sec*	*8/sec*	*12/sec*	*16/sec*	*20/sec*
Capacitance vessel	9.1±1.2	13.3±1.6	19.5±1.4	24.5±1.9	32.09±2.38	37.08±1.7	36.81±0.9
Resistance vessel	9.5±0.9	13.7±0.6	19.9±0.5	25.4±1.4	37.7±1.2	52.9±2.1	67.5±2.7

*Data obtained from twelve exeriments in 6 dogs.
**Voltage and duration of stimulation pulses kept supramaximal at 7 volts and 1.5 msec respectively.

TABLE II*: Percentage decrease in the sympathetic chain induced cutaneous vessel responses following intravenous administration of phenoxybenzamine. Stimulation was done by 7V, 1.5 msec pulses at two different frequencies of 1 and 20 per sec.

			***Control*	*After phenoxybenzamine*				
				1 mg/kg	*3 mg/kg*	*5 mg/kg*	*7 kg/mg*	*10 mg/kg*	*15 mg/kg*
Capacitance Vessel	1/sec	100	81.24±5.55	66.6±3.23	57.97±3.87	46.65±5.20	32.30±4.10	27.97±2.85
	20/sec	100	62.97±5.50	55.02±5.3	44.27±4.47	33.50±4.58	29.45±4.33	27.40±2.50
Resistance Vessel	1/sec	100	77.02±5.29	57.45±5.19	35.24±4.04	29.22±3.40	23.07±3.74	22.00±2.80
	20/sec	100	70.24±4.50	45.40±5.10	34.65±5.10	23.35±3.60	26.35±3.60	24.25±3.88

*Data compiled from observations on eight dogs.
**Readings before the administration of the drugs were considered 100%.

*mm*Hg with stimulation at 20-24/sec. When frequency response curves were plotted in terms of the percentage of the maximum, the capacitance vessel curve however, stood slightly to the left of the resistance vessel curve (Fig. 3b). It will also be noticed that the systemic arterial pressure was not affected by these stimulations at any frequency.

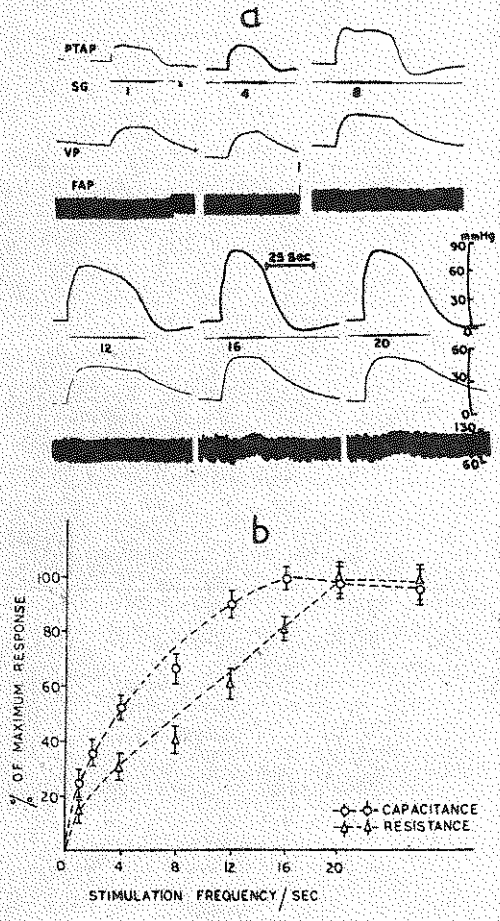

Fig. 3: (a): Effect of sympathetic chain stimulation (7V, 1.5 *m*sec) at successively increasing frequencies as indicated under each stimulation signal. PTAP - posterior tibial arterial pressure (occluded) SG - stimulation signal, VP - Saphenous venous pressure (occluded) FAP - Femoral arterial pressure. Increasing frequencies of the same stimulus pulses successively increased the magnitude of response of both capacitance and resistance vessels.

(b): Frequency - Response curves of the capacitance and resistance vessels plotted from the data obtained from 12 experiments of the type depicted in Fig. 3(a). The frequency response curve for the capacitance vessel is a little to the left of that for the capacitance vessel. Otherwise they both follow the similar pattern.

Effect of adrenergic blocking agents (Fig. 4): While assessing the effect of alpha-adrenergic blocking agent phenoxybenzamine on these responses, it was noticed that both resistance and capacitance vessel responses were almost equally affected. The magnitude of the response blockade was directly proportional to the dosage of phenoxybenzamine. This relationship existed irrespective of the frequency of sysmpathetic chain stimulation (Table II). In none of the experiments a complete blocking of the response was produced even after a cumulative dosage of 15 *mg/kg* of phenoxybenzamine. The residual response remained at 27% for the capacitance vessel and about 22-24% for the resistance vessel after this dosage of phenoxybenzamine. In

all cases, however, the noradrenaline reversal effect on the systemic arterial pressure was observed after the administration of phenoxybenzamine at 7-10 *mg/kg*. A consideration of Fig. 4 and Table II also brings home that the blocking effect of phenoxybenzamine on the resistance vessel

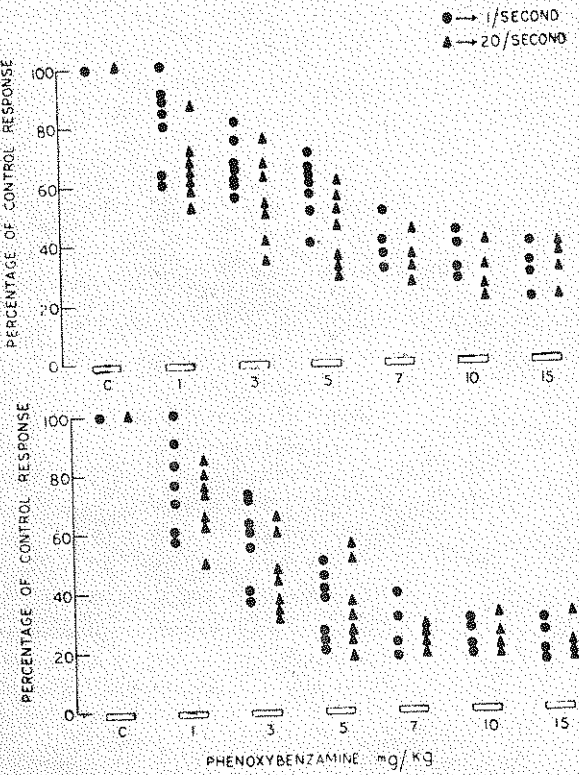

Fig. 4: Effect of phenoxybenzamine on responses of capacitance and resistance vessels obtained at two different frequencies (1/sec and 20/sec) of sympathetic chain stimulation. Responses of both vessels show a successive diminution with increasing doses of phenoxybenzamine irrespective of the frequency of stimulation. The decrease in the resistance vessel response however is obtained earlier than that of the capacitance vessel response. Upper plot is for capacitance vessels and the lower one is for resistance vessels. Note also that the responses of any vessel are never completely blocked even though the cumulative dosage of phenoxybenzamine is as high as 15 *mg/kg*.

response occurs quicker *i.e.* at smaller dosage when compared to that on the capacitance vessel response. Administration of beta adrenergic blocking agent propranolol in dosage sufficient to block the isoprenaline (1-2 $\mu g/kg$) induced fall in systemic arterial pressure and heart rate did not affect the resistance and capacitance vessel response in any experiments.

Fig. 5 depicts a series of records of the occluded limb capacitance and resistance vessel responses obtained on sympathetic chain stimulation after the injection of four successive doses of 1 *mg/kg* phenoxybenzamine showing a successive diminution of responses of both the vessels. It will be noticed that in each test there was also a successive diminution of the systemic arterial pressure and the cardiac responses induced by the administration of 0.25 $\mu g/kg$ of norepinephrine. Propranolol (1 *mg/kg*) administration though effectively blocked the isoprenaline (1 $\mu g/kg$) induced fall in systemic arterial pressure, did not change the neurogenically induced capacitance and resistance vessel responses in any manner.

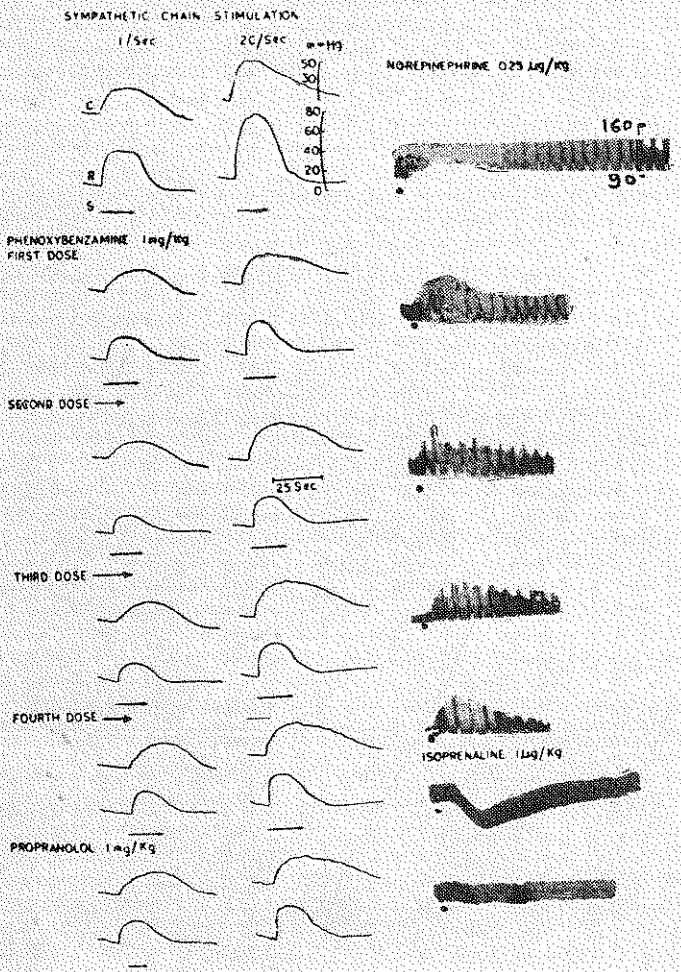

Fig. 5: Depicts the actual records of an experiment of the type from which data depicted in Fig. 4 was obtained. Note that phenoxybenzamine 1 *mg/kg* at four successive doses equally reduced the responses of capacitance and resistance vessels obtained on stimulation of sympathetic chain both at 1/sec and 20/sec. Similarly it also reduced the systemic arterial pressure response to 0.25 µg *i.v.* norepinephrine (extreme right column). Also note that administration of propranolol 1 *mg/kg* did not affect the sympathetic chain stimulation responses in any manner although the systemic arterial pressure response to isoprenaline (1 µg/*kg*) was completely blocked.

DISCUSSION

The increase of capacitance vessel pressure in the occluded limb obtained on stimulation of sympathetic chain is essentially due to the active constriction of the capacitance vessel itself. It could not be a reflection of the changes in the pre-capillary resistance vessels because after the circulatory arrest the equilibrium pressure of the capacitance vessel (10-30 *mm*Hg) was always higher than that of the resistance vessel (5-10 *mm*Hg). It has been reported that passive increase in the capacitance vessel tone generally occurs only at pressures lower than the equilibrium pressure achieved in this tudy (24). The reactivity of resistance vessel to sympathetic stimulation decreases with the progress of ischaemic changes resulting from circulatory arrest. This is in contrast to the relative immunity against ischaemia enjoyed by the capacitance vessels. Never-

theless, this technique was found to be equally useful for measuring changes in the resistance vessel tone because the decrease in the reactivity of these vessels was proportional to the period of circulatory arrest. Thus a sufficiently accurate analysis of increase in their pressure on sympathetic stimulation was obtained by extrapolating the recorded pressure increase to the 100% level at 0 time of circulatory arrest (Fig. 1).

In the present study the sympathetic chain was stimulated at lumbar 4-5 because it has been documented that the sympathetic fibres to the hind limb of dog leave the cord in the spinal nerves at 1-4 lumbar level and that stimulation of sympathetic fibres at lumbar 4-5 produces maximum constriction of capacitance, resistance and shunt vessels of the hind limb and marked increase in the resistance to hind limb cutaneous blood flow (4,5,7).

Graded increase in the sympathetic discharge obtained by step-wise increase in the stimulation frequency produced corresponding increase in pressure of both resistance and capacitance vessels. These findings are similar to some observations of earlier authors (4,21). Our findings further show that if the observations are restricted to the cutaneous vessels, the upper limits of frequency which produce the maximum constriction in these vessels are a little higher than those obtained by these authors *i.e.* 16-20/sec. In line with Mellander (21) it was also observed that the frequency response curve of the capacitance vessel was a little to the left of that of the resistance vessel. This was essentially because of the fact that the maximum of the capacitance vessel response was achieved at frequencies which were a bit lower than those required for the maximum of the resistance vessel response. Otherwise at lower frequencies the pressure rises in both types of vessels were of similar magnitiude (Table 1).

Mellander (21) as well as Oberg (23) observed that sympathetic stimulation leads to the influx of interstitial fluid into the blood vessels. This was considered to be due to the comparatively more increase in the tone of resistance vessels than that of capacitance vessels. In the light of our observations such an influx should be more conspicuous at higher frequency of stimulation *i.e.* higher level of sympathetic discharge. Direct observations with the help of a microscope and measurement of segmental flow resistance, however, has demonstrated that sympathetic stimulation leads to the flux of fluid in the opposite direction *i.e.* from vessels into the interstitial spaces (15,16). A closer look at the papers of these authors shows that they are actually observing the fluid flux immediately a after the sympathetic stimulation. Such a transport of fluid from the vessels into the intestitial spaces during the post-stimulatory phase is also observable from the records of Mellander (21) and Oberg (23). In this study it is demonstrated that though the rate of pressure rise on syspmathetic stimulation is similar in both capacitance and resistance vessels, the rate of post-stimulalory pressure fall is much slower in the capacitance vessel as compared to the resistance vessel. Evidently such a discrepancy leading to a comparatively more pressure in the capacitance vessel than the resistance vessel just after sympathetic stimulation will facilitate the transport of fluid from the vessels into the tissues.

The concept of there being two types of adrenergic receptors on the vessel wall *i.e.* alpha and beta is essentially based on the blockade of the responses of exogenously administered alpha-stimulants like norepinephrine and beta-stimulants like isoprenaline with their respective blocking agents (9, 10, 11, 13, 14, 18, 22, 28, 29). It has been recently reported that norepinephrine reflexely released at the sympathetic nerve endings in the arterial bed of muscle cirulation acts only on the alpha receptor (12). Our observations with respect to the cutaneous circulatory bed are similar. The neurogenically released norepinephrine in these experiments engaged mainly the alpha receptors which was true for veins as mush as for arteries. No evidence was found for the noradrenaline released on sympathetic nerve endings having any action on the beta receptors. The blockade of the response of both types of vessels by phenoxybenzamine, however, was never complete even when the dosage was as high as 15 *mg/kg*. Such a situation existed regardless of the frequency of sympathetic stimulation. The norepinephrine induced increase in systemic arterial pressure however, was always blocked completely at that dose level of phenoxybenzamine. This possibly means that at least with respect to the cutaneous vessels some receptor sites which get engaged by neurogenically released norepinephrine remain inaccessible to the circulating blocking agents. These observations are in consonance with the current pharmacological concept of differentiating between the adrenolytic and sympatholytic agents (22), although some authors have recently reported equally effective blockade of the responses of norepinephrine and the neurotransmitter-norepinephrine (2,3). These authors also reported the phenoxybenzamine blocks the capacitance vessel response more effectively than the resistance vessel response which meant the facilitation of fluid transport from tissues to vessels. The plasma expanding action of phenoxybenzamine when administered in shock was explained on this basis. However, we find that phenoxybenzamine blocks equally the respocnses both of capacitance and resistance vessels. Possibly the plasma expanding action of phenoxybenzamine, as some of out studies indicate (20) is through its effect on the central nervous system.

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