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THE EFFECT OF SEROTONIN INJECTED INTRA-ARTERIALLY ON THE CUTANEOUS NERVE ADDITIONALLY CONTRASTED WITH NOR-EPIRENAMINE

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Serotonin has been reported to be a pain-producing substance and confiremed to cause the cutaneous nervous discharge by the arterial injection. On the other hand, serotonin has an obvious effect on blood vessels. The relationships among the above three facts derived from serotonin action have not been yet clarified. In the present paper, the auther intended to investigate the nature of the discharge in rabbit's saphenous nerve from the aspect of blood circulation change by the injection of serotonin into the femoral artery and contrasted with that of nor-epirenamine.

Serotonin evoked the bimodal discharge enhancement in dose, which have an effect on the blood pressure. On the injection of a mixture of serotonin and nor-epirenamine, both were compensated by each other and the blood pressure alternation was not observed, but the first phase of the enhancement remained.

This phase appeared soon after the injection and was intensified by venous occlusion. Neither blood pressure change nor the second enhancement was observed with the venous occlusion, but in larger dose, the second one was evoked coincidently with the blood pressure change after the release of occlusion. Then, the second enhancement was considered to be closely related with the blood pressure change.

The discussion was particularly directed to the existence of baroreceptor of the peripheral blood vessels.

Serotonin on the human blister base caused the pain sensation in the low concentration (10^{-3}–10^{-8} g/ml) (Armstrong *et al.*[1] 1953). Reid[2] (1952) described that the intradermal injection of 5-HT caused the flush of skin but no pain nor itching. Douglas and Ritchie[3] (1957) found that 5-HT was potent for the cutaneous fibre stimulation. Fjällbrant and Iggo[4] (1961) described that the close arterial injection of 5-HT (4–40 μg) caused the impulse discharge on the cat's cutaneous afferent fibre within 20 sec and reached the peak frequency 1–3 min after the injection. All these papers represent that serotonin could induce the peripheral action.

Furthermore, the effects of serotonin on the blood pressure are various, that is, serotonin acts directly as a vasoconstrictor and cardiac stimulant but

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the response largely depends upon the dose, anesthetics, neurogenic vasoconstrictor tone and animal species (Page[5] 1958). Roddie *et al.*[6] (1955) demonstrated that serotonin constricted the arterioles and at the same time dilated the minute vessels of the skin. Haddy *et al.*[7] (1957) also reported that, in the dog's foreleg under pentobarbital anesthesia, nor-adrenaline contracted the small vessels but serotonin dilated the minute vessels in spite of increase of small vessel resistance.

It is very interesting to relate the effects of serotonin on the cutaneous nerve to that on the blood vessel and contrast with those of nor-epirenamine.

In the present investigations, it was attempted to record simultaneously the electrical activity of the rabbit's cutaneous nerve and the systemic blood pressure alternation induced by the close arterial injection of serotonin or non-epirenamine.

METHODS

Twenty four healthy adult rabbits weighing 2.5–3.0 kg were anesthetized with Nembutal sodium solution (pentobarbital sodium, about 25 mg/kg body weight, intravenously), fixed on their back and incised at the medial skin surface of the hindpaw under the knee joint. The major saphenous nerve was exposed, cut and divided into three or more nerve strands containing about 30–40 fibres. The peripheral stump of one of these strands was placed on the bipolar silver wire electrodes (tip diameter was 0.15 mm), through which the electrical activity was led to the C-R coupling amplifier, observed with a cathode ray oscilloscope and analized by the recorded data. The receptive fields of these nerves were confirmed by touching the skin lightly with the small glass rod. Those were localized from the middle of the leg to the medial malleolus. The hair of the leg was sheared carefully so as that the impulse discharge may not be produced by an air blow.

The femoral artery was exposed in the groin and chemicals were injected into the saphenous artery through the femoral artery by a fine needle and other branches of the artery were ligated as far as possible.

The systemic blood pressure was recorded simultaneously on the contralateral femoral artery through the catheter filled with heparinized saline connected to an electric manometer.

The chemicals used in these experiments were serotonin-creatinine sulfate and dl-nor-epirenamine.

RESULTS

A. Resting discharge

Rabbit's major saphenous nerves were dissected into three or more nerve strands, which were composed of about 30–40 nerve fibres.

The conducted impulses along these multi-fibre strands were recorded.

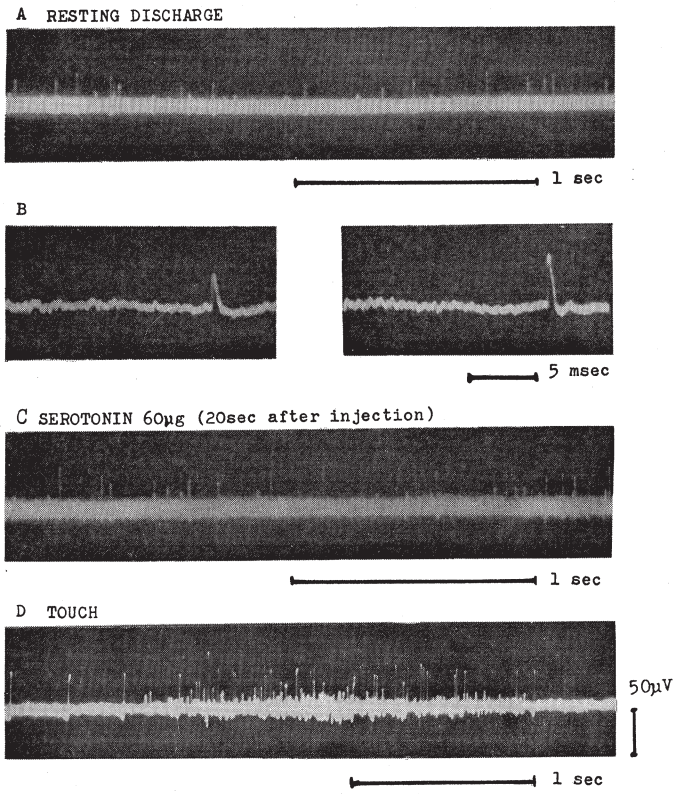

FIG. 1. A.: The resting discharge in the multi-fibre strand of the rabbit's major saphenous nerve. This is a part of the continuous recording. B: The record from the same strand. The sweep velocity was 62.5 times of that of A. C: The record of the discharge enhancement caused by the injection of serotonin 60 μg. The top of this record correspond to the time of 20 sec. after the beginning of the injection. D: The burst of discharge elicited by the mechanical stimulation. The skin was touched at the receptive field lightly by the glass rod (tip diameter: 1 mm).

The average frequency of the resting discharge was 2.7 impulses/200 msec. (range: 1–7 impulses/200 msec.). Fig. 1. A. shows the resting discharge of these strands and the individual impulses were demonstrated in Fig. 1. B.

The mechanical stimulation of the receptive field caused the burst of impulse discharge in these strands (Fig. 1. D.).

The resting discharge changed according to conditions of anesthesia and others in every preparation.

B. Intra-arterial injection

After the peripheral stump of the major saphenous nerve strand had been placed on the recording electrodes, sertonin and nor-epirensmine solutions which contained 100 μg of the chemicals in 1 ml saline respectively, was in-

jected into the femoral artery. The infusion required about 10–20 sec., because the fine needle had been employed in order to prevent bleeding after the injection.

Serotonin 2–5 μg: Neither discharge enhancement nor blood pressure change was occurred in any case.

Serotonin 10 μg: In two cases, no discharge enhancement was occurred and in another one, there was the unimodal discharge enhancement with the peak frequency which reached 3.0 times of the resting value 60 sec. after the injection. But, in all cases, no blood pressure changes were observed.

Serotonin 20 μg: In most cases, the discharge was enhanced up to 3.5–4.0 times of the resting 35–45 sec. after the injection and then returned to the resting discharge of 2–3 impulses/200 msec. 50–55 sec. later. No blood pressure change was produced with these doses. Fig. 2. A. represents one of these discharge enhancements. In this case, the discharge frepuency began to increase soon after the injection of serotonin, reached its peak 35 sec. later and decreased the frequency gradually.

Serotonin 40 μg: In most cases, there were the bimodal discharge enhancements and their first peak was 19–25 sec. after the injection and the second peak was 43–51 sec. after the injection (24–26 sec. after the first peak).

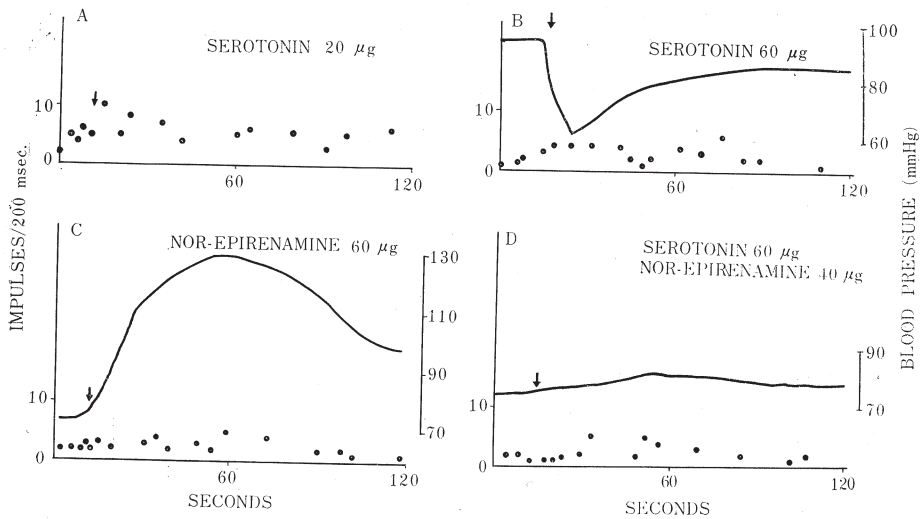

FIG. 2. A: The unimodal discharge enhancement induced by the intra-arterial injection of serotonin 20 μg in the multi-fibre strand. B: The bimodal discharge enhancement and the alternation of the maximum blood pressure (above) elicited by the injection of serotonin 60 μg. C: The discharge enhancement and remarkable rise of the maximum blood pressure (continuous line) elicited by the injection of nor-epirenamine 60 μg. D: The unimodal discharge enhancement and flatted blood pressure change caused by the injection of serotonin 60 μg and nor-epirenamine 40 μg.

The discharge frequency of the first peak was 1.2–5.0 times of the resting and the second was 1.8–5.0 times. In the half of these cases, there was no blood pressure change, but in the other half, the sustained blood pressure fall was observed following sustained discharge enhancement.

Serotonin 60 μg: The bimodal discharge enhancements which had the peaks at 41–55 sec. and 50–93 sec. after the injection, were elicited in most cases and their peak frequencies were 1.2–9.0 and 2.7–9.0 times of the resting.

The blood pressure began to fall 13–14 sec. after the injection and reached their minimum pressure 25–26 sec. after the injection and then returned to the resting level gradually in about 45 sec. The discharge enhancement began soon after the injection, but the blood pressure began to fall 13–14 sec. after the injection. Fig. 1. C. shows one of these discharge enhancements 20 sec. after the injection. Fig. 2. B. represents the time course of this bimodal discharge enhancement, that is, the discharge was enhanced soon after the injection. Then, the frequency decreased and backed to the resting level 49 sec. after the injection. Then the discharge began to increase again and reached the second peak 76 sec. after the injection. The blood pressure began to fall remarkably 13 sec. after the injection and showed the minimum pressure 12 sec. later and followed by the sustained fall.

Nor-epirenamine 5 μg: Neither discharge enhancement nor blood pressure change was observed in any case.

Nor-epirenamine 10–20 μg: The discharge was enhanced up to 2.0–2.3 times of the resting and the blood pressure began to rise at 13–15 sec. after the injection and the maximum pressure was higher than the resting by 10–20 mmHg.

Nor-epirenamine 60 μg: The chemical was injected into the femoral artery during 11–20 sec. The discharge enhancement was elicited about 15–30 sec. after the beginning of the infusion. The discharge frequency reached the maximum, which was 2.5-3.0 times of the resting, at 50–70 sec. after the injection and returned gradually to the resting.

The blood pressure began to rise 9–14 sec. after the injection and reached the maximum pressure 50–75 after the injection. The amount of the pressure change varied from 19 to 56 mmHg with the preparations. The time course of the discharge enhancement was similar to that of the blood pressure change. Fig. 2. C. demenstrates the result of one of these experiments. The discharge was enhanced gradually and reached the peak 59 sec. after the injection. The blood pressure began to rise remarkably and attained to the maximum 57 sec. after the injection.

C. Combined injection of serotonin and nor-epirenamine

Mixed solutions of serotonin 60 μg and nor-epirenamine 40 μg were infused into the femoral artery for 9–21 sec. in eight cases. The discharge enhance-

ment was unimodal. At first, the discharge frequency gradually increassed and showed the peak frequency of 2.5–3.5 times of the resting 44–69 sec. after the beginning of the injection. In two cases, there were sustained discharge enhancements, but in the other six cases, the discharge enhancement returned to the resting level 14–15 sec. later. No blood pressure change was observed in 75% of the cases examined, in the other cases, the infusion caused the slight rise of blood pressure and bradycardia, but the amount of the pressure rise was less than 8 mmHg. The type of the blood pressure change was different from the remarkable fall in serotonin infusion and also from the rapid rise in nor-epirenamine infusion. The enhancement corresponding with the second mode of the bimodal discharge enhancement which was observed in the case of serotonin 60 μg infusion is considered to have disappeared in thess experiments, because there was no blood pressure change. Fig. 2. D. demonstrates an example of these experiments.

The discharge was enhanced gradually and reached the peak 50 sec. after the injection. The blood pressure rose slowly, but the maximum was only 8 mmHg above the resting level 50 sec. after the injection.

D. Intra-arterial injection conditioned with the venous occlusion

The common iliac vein was occluded with the clip and the chemicals were infused into the homolateral femoral artery. Then the occlusion was released quickly 30–51 sec. after the beginning of the injection (18–31 sec. after the end of the infusion).

Serotonin 20 μg: The unimodal discharge enhancement was observed in all four cases. The discharge frequency became 1.8–2.3 times of the resting 8–12 sec. after the injection, gradually decreased and returned to the resting level 60–81 sec. later. The blood pressure did not change in any case. Another peak of discharge enhancement was not obtained in serotonin 20 μg infusion.

Fig. 3. A. shows one of these instances. The discharge frequency was enhanced steeply and reached the maximum 5 sec. after the beginning of the injection, successively making the plateau for 30 sec. The venous occlusion was released 39 sec. after the injection and enhanced discharge decreased slowly to the resting level. Only one peak of enhancement was observed in this case and the blood pressure remaiened unchanged.

Serotonin 60 μg: The discharge frequency reached the maximum 9–29 sec. after the beginning of the injection and its frequency was 2.0–9.0 times of the resting, then maintaining a plateau for a while and gradually decreased its frequency. The venous occlusion were released 33–38 sec. after the beginning of the injection and the discharge returned to the resting level 16–24 sec. later.

Again, the discharge increased and became 1.7–6.5 times of the resting 23–37 sec. after the release of venous occlusion. No blood pressure change was observed during the venous occlusion. The blood pressure began to fall 2–3

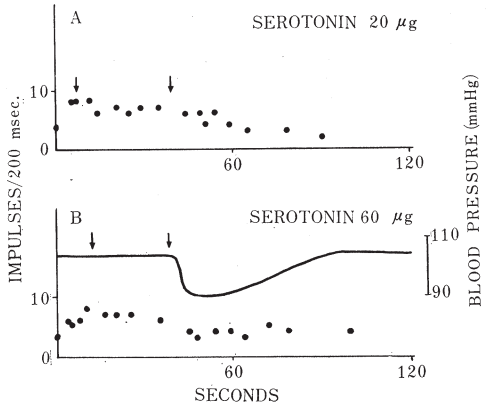

FIG. 3. When the common iliac vein was occluded, serotonin 20 μg (A) and serotonin 60 μg (B) were injected into the femoral artery and the injection ended at the first arrow. The discharge enhancement shows a plateau (A and B) and the blood pressure not changed (B). The venous occlusion was released at the second arrow and the blood pressure began to fall in B. The blood pressure change not observed in A.

sec. after the release of the venous occlusion and showed the minimum 3-4 sec. later. The amount of the blood pressure fall from the resting was 7-13 mmHg and these were smaller than that with the arterial injection of serotonin 60 μg without venous occlusion. The blood pressure showed the sustained fall and returned to the resting 65-95 sec. later.

In Fig. 3. B., one of these examples is demonstrated. The discharge was enhanced steeply and reached the peak frequency 10 sec. after the beginning of the injection and maintained almost the same discharge level for 25 sec. and then gradually decreased. At 38 sec. after the begining of the injection, the venous occlusion was released. The blood pressure began to fall repidly 2 sec. after the release of the venous occlusion and reached the minimum 10 sec. later and then returned gradually to the resting level. The dischrge fell to the resting level 8 sec. after the release of the venous occlusion, then the frequency increased slowly and reached the second peak 24 sec. later.

Nor-epirenamine 60 μg: 60 μg of nor-epirenamine was infused for 15-20 sec. The discharge was enhanced gradually and reached its peak frequency, 1.1-2.7 times of the resting at 24-29 sec. after the begining of the injection and returned to the resting level 32-42 sec. later. The venous occlusion was released 30-50 sec. after the injection. The discharge frequency was enhanced again getting to 1.8-3.0 times of the resting 4-25 sec. after the release of the venous occlusion. In 25% of these cases, there was no blood pressure change, but in the other cases, the blood pressure began to rise remarkably after the release of the venous occlusion, then the pressure showed the maximum 15-21 sec. later. The time course of the second elevation of frequency enhancement was similar to that of the blood pressure change.

E. Single unit discharge

In seven preparations, the impulse discharges were recorded from fine nerve filaments of rabbit's saphenous nerve. The recorded electrical activities were fairly enough to be denoted as single unit discharge.

Serotonin 60 μg: Fig. 4. shows one of these cases, in which the arterial injection of serotonin 60 μg evoked the enhancement of discharge population. The discharge frequency was increased gradually and the frequency histogram per 2 sec. had its peak 50 sec. after the injection. The peak frequency amounted to 2.8 times of the beginning, and in the cases of single unit discharge the enhancement was all unimodal. This fact would suggest that the bimodal discharge enhancement caused by the arterial injection of

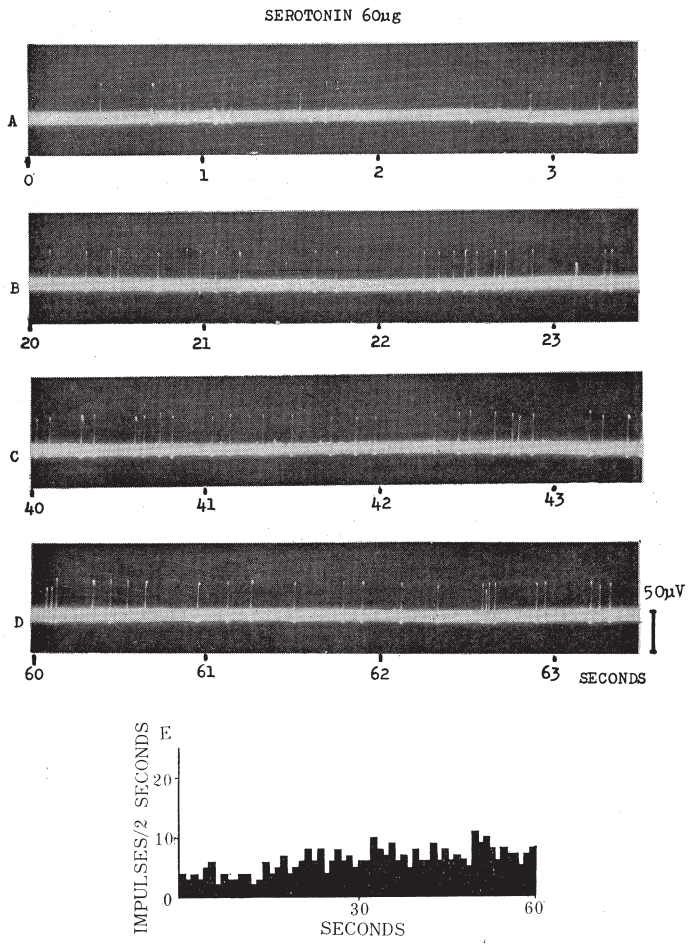

FIG. 4. A: The resting discharge of the fine nerve strand (single unit discharge). B, C, D: The enhanced discharge 20 sec. (B), 40 sec. (C), 60 sec. (D) after the injection of serotonin 60 μg. E: the histogram of the discharge frequency per 2 sec.

serotonin 60 μg in multi-fibre preparation was composed of the dischrges of probably two or more kinds of fibres. Further it is conceivable that the first mode in the bimodal enhancement in the multi-fibre preparation would disappear in present cases.

Nor-epirenamine 60 μg: Fig. 5. demonstrates that the infusion of nor-epirenamine 60 μg enhanced the discharge. The frequency per 2 sec. histogram had its peak 10 sec. after the injection and the maximum discharge frequency was 4.0 times of the resting. The enhanced discharge was rapidly adapted and backed to the resting about 35 sec. after the injection.

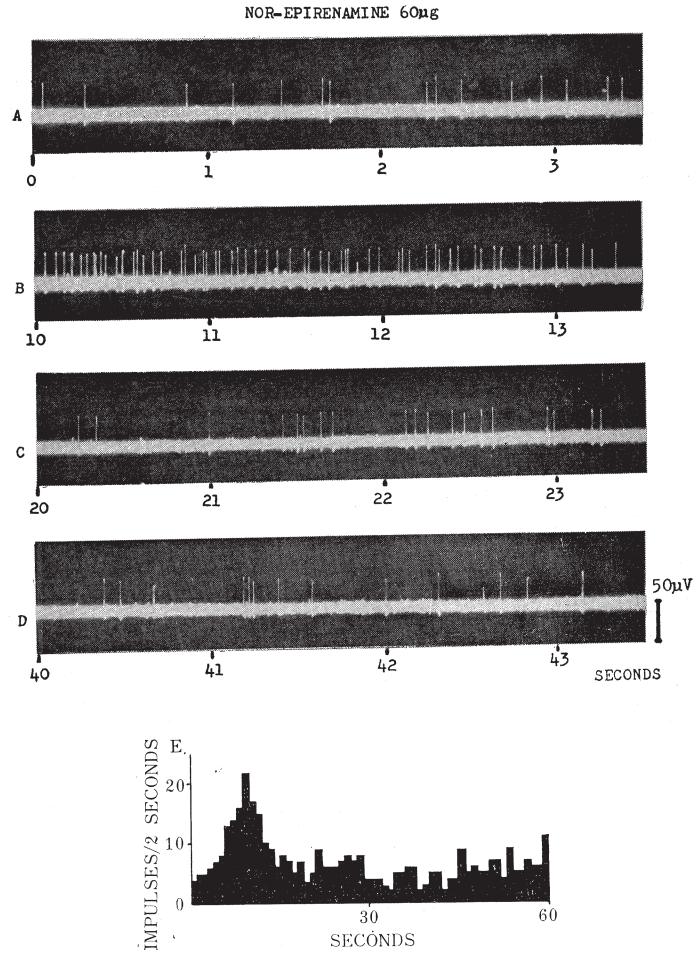

FIG. 5. A: The resting discharge. B, C, D: The discharge enhancement elicited by nor-epirenamine 60 μg 10 sec. (B), 20 sec. (C), 40 sec. (D) after the injection. E: The frequency histogram per 2 sec. of the enhanced discharge.

F. Intravenous injection

In the preliminary experiments, serotonin and nor-epirenamine were injected into the preauricular or retro-auricular vein. No discharge enhancement was elicited by the injection of serotonin 10 μg, 30 μg of serotonin induced the discharge enhancement and, in doses of 40–50 μg, the enhancement was remarkable. In some cases, the discharge enhancement reached the maximum 1 min. after the end of the injection and the discharge frequency was 3.0 times of the resting. Generally, the discharge decreased temporarily soon after the end of the injection, then gradually increased and reached the peak about 1–2 min. later. The injections of nor-epirenamine 50 μg elicited the discharge enhancement with the peak about 15–30 sec. after the end of the injection. Fig. 6 demonstrates the discharge enhancement induced by the intravenous injection of serotonin 50 μg (A) and nor-epirenamine 50 μg (B).

Table 1. represents the results of a series of experiments carried out by auther. It was shown that the amount of the blood pressure alternation elicited by both the arterial injection provided with venous occlusion was less than that without venous occlusion. This suggésts the inactvation of chemicals in the peripheral tissues.

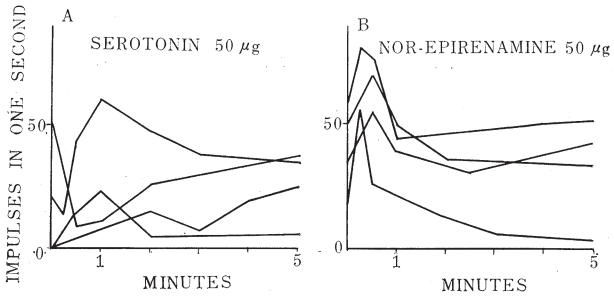

FIG. 6. The discharge enhancement elicited by the intravenous injection of serotonin 50 μg (A) and nor-epirenamine 50 μg (B).

DISCUSSION

Fjällbrant and Iggo[4] (1961) reported that the close arterial injection of 5-HT (4–40 μg) into the cat's saphenous artery caused the discharge enhancement in the multi-fibre strand of the saphenous nerve which reached its peak 1–3 min later and in the single afferent fibre préparation, they found that some myelinated afferent fibre were affected by 5-HT (1–20 μg): the resting discharge was enhanced bimodally. Also the response of some non-myelinated fibre to the mechanical stimulation showed the bimodal discharge enhacement and the second phase was observed during the recovery process from the effect of 5-HT.

Douglas and Ritchie[8] (1957 e) demonstrated that 5-HT evoked the discharge

TABLE 1. The number of "Peak time" shows the time in sec. after the beginning of the injection but the second peak of the arterial injection with venous occlusion shows the time after the release of occlusion (*)

	Discharge enhancement Type	Peak time	Blood pressure change Type	Amount
Arterial injection				
Serotonin				
2 μg	nil		unchanged	
5 μg	nil		unchanged	
10 μg	nil (2 case)		unbhanged	
	unimodal	60 (1 case)	unchanged	
20 μg	uhimodal	35-45	unchanged	
40 μg	bimodal	19-25 and 43-51	unchanged (50%)	
			fall (50%)	16-18 mmHg
60 μg	bimodal	41-55 and 50-93	fall	17-30 mmHg
Nor-epirenamine				
5 μg	nil		unchanged	
10 μg	unimodal	22-41	rise	10-15 mmHg
20 μg	unimodal			
60 μg	unimodal	50-70	rise	19-56 mmHg
Mixture				
Serotonin 60 μg and nor-epirenamine 40 μg	unimodal	44-69	rise slightly (25%)	
			unchanged (75%)	
Arterial injection with venous occlusion				
Serotonin				
20 μg	unimodal plateau		unchanged	
60 μg	bimodal	9-29 and 23-37* (plateau)	fall	7-13 mmHg
Nor-epirenamine				
60 μ	bimodal	24-29 and 4-25*	rise (75%)	5-45 mmHg
			unchanged (25%)	

on the C_1 group fibre of the cat's saphenous nerve when it was injected close-arterially, but they could not dicide whether 5-HT stimulatilated the C fibre ending directly or acted indirectly through the intervention of the smooth muscle and suggested that the direct action was not improbable because of the evidence that this effect was caused in the carotid body or other receptor site.

In the present experiments, the discharge enhancement with two phases occurred in almost all cases of the intra-arterial injection of serotonin 40-60 μg, but 20 μg or less of serotonin aroused the unimodal discharge only. In these experiments in multi-fibre strand of saphenous nerve, it was unable to dicide the particular active fibre.

In the experiments carried out by Ejällbrant and Iggo[4] (1961), the blood stream of the femoral artery was stopped during the injection of the chemicals, whereas in the present auther injected and infused the chemicals into the femoral artery in which the normal blood stream was maintained. Therefore, the time courses of the discharge enhancement in these two cases are con-

sidered different from each other, and the bimodal discharge enhancement was remarkable in the latter. It may be said that the blood pressure alternation was not remarkable because that the chemicals injected into the artery, in which the blood stream had been stopped, should have been destroyed in the peripheral blood vessels and so serotonin could not give effect on the blood pressure.

Generally, the time course and intensity of the discharge enhancement exhibited considerable variation with the preparation. But, it is evident that the close-arterial injection of serotonin 40-60 μg causes the discharge enhancement with two phases. The second mode of the enhancement would be related partly to the alternation of the systemic blood pressure, that is, these enhancements were observed during the recovery time from the blood pressure fall induced by serotonin infusion. This assumption woulod be supported by the evidence that the second mode of enhancent was not observed in the cases without the blood pressure alternation, which was elicited by the intra-arterial injection of serotonin 5-20 μg or simultaneous injection of serotonin 60 μg and nor-epirenamine 40 μg. The plateau of the first discharge enhancement induced by serotonin 60 μg with venous occlusion seems to suggest that the peripheral action of serotonin is prolonged by the interruption of the blood stream. The first enhancement seemed to depend upon the peripheral action of serotonin, because this enhancement has been elicited by a small dose of serotonin (5-20 μg) or the simultaneous injection of serotonin 60 μg and nor-epirenamine 40 μg. In the single unit preparation, in most cases serotonin caused the unimodal discharge enhancement and its time course was like that of the second mode of the discharge enhancement observed similarly in the muti-fibre strand.

Reid[2] (1952) reported that the intravenous injection of 5-HT caused the initial steep fall of the blood pressure and elicited the pressor response later. He suggested that the latter response was caused by the liberation of adrenaline from the suprarenal gland. Also, he described that the injection of 5-HT 1 μg into the femoral artery transiently increased the blood flow from the femoral vein and then decreased it corresponding to the pressor response.

Douglas and Toh[9] (1953) observed the blood pressure alternation of the dog's femoral artery caused by the intravenous injection of serotonin into the femoral vein and intra-arterial injection into the superficial branch of femoral artery under the penotobarbitone anesthesia. They described that, by the intravenous injection of serotonin 10 μg or less, the blood pressure began to fall 10 sec. after the injection and showed a descent of 40 mmHg later, but the large dose of serotonin produced the pressor effect. By the injection into the femoral artery, they observed that 100-200 μg of serotonin caused the small pressor response 10 sec. after the injection and, in their cases, there were increased latency (6 sec.) corresponding to the circulation time in the

limb.

The latency increase by the arterial injection was observed in the present experiments, and the blood pressure began to fall 13–14 sec. after the injection.

No pressor response was observed when the common iliac vein was occluded. As the discharge enhancement was remarkable when the vein occluded, it is evident that serotonin has a peripheral action.

In the observation of human peripheral blood vessels, Roddie, Shepherd and Whelan[6] (1957) found a sensation of tingling and the decrease of skin blood flow caused by the infusion of 5-HT 4–16 μg per minute. They suggested that 5-HT constricted the arterioles and at the same time, dilatated the minute vessels of the skin.

Page and McCubbin[10] (1956), in dogs and cats, observed that the intravenous infusion of serotonin evoked the sustained pressure fall of the femoral artery.

These depressor response was reduced or prevented with the anti-histamine drugs. From this evidence, they suggested that serotonin would release histamine locally. Further they observed the pressor response moderately increased by nor-adrenaline during the infusion of serotonin. But in the present experiments, when serotonin and nor-epirenamine were injected simultaneously, the depressor response of serotonin and pressor response of nor-epirenamine were compensated each other so that the blood pressure remained almost unchanged. In general, the effect of serotonin on arterial pressure is result of peripheral and cardiac actions.

It was described by Douglas and Ritchie[11] (1959) that histamine caused itch sensation, when it was pricked into the skin, but no obvious nervous discharge was evoked by the close-arterial injection. In the present experiments, the discharge enhancement was induced by the injection of serotonin, though an anti-histamica (dimethyl aminoethyl ether: 20 mg) was injected intramuscularly 10 min before the experiment. From this evidence, it seems likely that the discharge enhancement by serotonin was not mediated by histamine action.

In auther's experiment of the intravenous injection into the preauricular or retroauricular vein, serotonin 30 μg or more or nor-epirenamine 50 μg induced the retarded discharge enhancement.

In the foreleg of pentobarbital anesthetized dog, Haddy *et al.*[7] (1957) observed that nor-epirenamine increased the total vascular resistance primarily through small vessels constriction and it also constricted large artery and vein. But, serotonin did not significantly change the total resistance, in spite of dilating small vessels. The faradic stimulation of sympathetic nerve constricted all vascular segments and nor-epirenamine caused the active contraction of all segments. If serotonin has an effect on the sympathetic nervous system, it should appear the constriction of all vascular segments, but Haddy's experiment showed that serotonin dilated small vessels.

About 20% of the non-myelinated fibre in the cat's saphenous nerve were sympathetic motor fibre (Heinbecker *et al.*[12], 1933). Although, it is improbable that, when serotonin is injected close-arterially, it stimulates the sympathetic nerve fibre, because serotonin stimulates the peristalsis of small intestine, namely antagonistic against the sympathetics.

Weddell *et al.*[13] (1959) observed histologically that some free nerve ending lay among the blood capillaries and venules in the dermis of human hairy skin and these terminals served by non-myelinated or thin myelinated fibres. The great majority of the latter are less than 6 μ in diameter.

The diameter histogram of the rabbit's saphenous nerve strand had two peak at 2-3 μ and 6-7 μ, respectively (Fig. 7.). The conduction velocities of the impulses caused by serotonin 60 μg in multi-fibre strand were measured and their distribution had the peak at 1.4 meter/sec. (the range was 1.3-1.6 m/sec.) and 9.3 meter/sec. (7.6-13.7 m/sec.). The latter value corresponed to δ_2 fibre (8-17 m/sec., Zottermann[14], 1939), which have been brought into the activity by noxious, touch, cooling or warming stimulation of the skin.

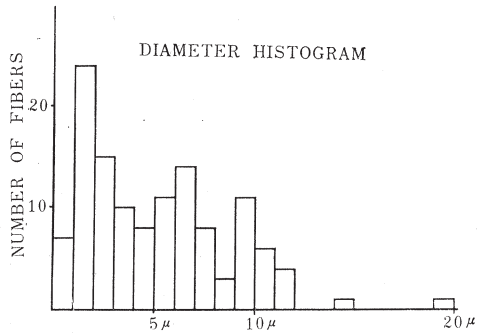

FIG. 7. The diameter histogram of a multi-fibre strand of the major saphenous nerve.

What meaning have the cutaneous nervous discharge caused by such drugs as serotonin, nor-epirenamine or histamine? It is known that the baroreceptor in the carotid sinus of cat is excited by small amounts (2-10 μg) of 5-HT and produces a fall of blood pressure. And it was suggested that this hypotensive effect of 5-HT might be due to constricting the vascular wall of carotid sinus and stimulating baroreceptor (Ginzel and Kottegoda,[15] 1654). The burning feeling (Page and McCubbin,[10] 1956) or the tinglingsen sation (Roddie *et al.*,[6] 1955) might be due to the early discharge by serotonin, but the later one has been verified to be evoked coinciding with the secondary blood pressure rise. The injection of small amounts of serotonin or combined injection of serotonin and nor-epirenamine could not produce the later discharge as well as blood pressure change.

It is not improbable that there are primordial type of baroreceptor, which are excited according to blood pressure alternation, in the minute vessels of the skin or nearby tissue.

SUMMARY

1. The discharge enhancement was recorded in the cutaneous fibre of the rabbit's saphenous nerve under Nembutal anesthesia during the close arterial injection of serotonin and nor-epirenamine into the saphenous artery.

Simultaneously, the systemic arterial blood pressure of the contralateral femoral artery was registered.

2. Serotonin (10-20 μg) caused the unimodal discharge enhancement without the blood pressure change. The peak frequency was 3.0-4.0 times of the resting 35-60 sec. after the injection.

3. Serotonin (40-60 μg) caused the bimodal discharge enhancement with two peaks, 19-55 and 43-93 sec. after the injection. The peaks of the discharge frequency were respectively 1.2-9.0 and 1.8-9.0 times of the resting. The blood pressure began to decrease quickly 13-14 sec. after the injection and it was followed by the sustained fall.

4. The infusion of nor-epirenamine (10-60 μg) enhanced the discharge gradually up to 2.0-3.0 times of the resting 50-70 sec. after the beginning of the injection. The blood pressure reached the maximum 50-75 sec. after the injection.

5. When the occlusion was applied at common iliac vein, the first discharge enhancement caused by serotonin 60 μg was somewhat distorted, making a plateau and the second one was postponded after the release of occlusion.

The second was 1.7-6.5 times of the resting 23-37 sec. after the release of venous occlusion. The blood pressure began to fall 2-3 sec. after the release of the venous occlusion and showed the sustained fall for a while.

6. The close-arterial injection of nor-epirenamine 60 μg with the venous occlusion caused the discharge enhancement, amounting to 1.8-2.7 times of the resting 24-29 sec. after the injection and the another enhancement (1.8-2.7 times of the resting) appeared at 4-25 sec. after the release of the venous occlution. In 75% of these cases, the blood pressure began to rise remarkably by the release of venous occlution.

7. The combined infusion of serotomin (60 μg) and nor-epirenamine (40 μg) caused the unimodal discharge enhancement and its frequency became to 2.5-3.5 times of the resting 44-86 sec. after the injection. There was no blood pressure change in 75% of these cases.

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