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CARDIOVASCULAR EFFECTS OF INTRAVENOUS INFUSIONS OF 5-HYDROXYTRYPTAMINE IN MAN

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Intravenous infusions of 5-hydroxytryptamine creatinine sulphate in doses of 1, 2, and 3 mg./min. of the salt into 42 normal subjects caused a dilator response of the forearm vessels, consisting of an initial transient increase in flow usually followed by a smaller but sustained increase. A fall in forearm flow was not seen. Heart rate was invariably increased and the increase preceded other changes by 10 to 20 sec. suggesting a direct effect on the heart. The sustained increase in flow probably represents a balance between the direct constrictor action of the drug and a secondary dilator effect. The blood pressure response was variable and it appeared unlikely that it was responsible for more than a small part of the forearm flow changes. Two subjects appeared to be abnormally sensitive to the drug.

5-Hydroxytryptamine has been shown to be a powerful vasoconstrictor substance, and its direct action on the smooth muscle of blood vessels has been demonstrated in isolated preparations, in animals and in man (Reid and Rand, 1951 ; Page, 1942 ; Reid, 1952 ; Roddie, Shepherd and Whelan, 1955). However, intra-arterial injection of 5-hydroxytryptamine into a limb, although it reduces the total blood flow, results also in a flushing of the skin, indicating dilatation of small vessels ; a similar flushing is seen in patients with carcinoid tumours when large amounts of 5-hydroxytryptamine are circulating in the blood stream (Roddie *et al.*, 1955 ; Thorson, Biörck, Björkman, and Waldenström, 1954). Furthermore, the variability of the blood pressure changes seen on intravenous infusions of 5-hydroxytryptamine (Page and McCubbin, 1953) suggests that it does not behave as a general overall vasoconstrictor substance.

In order to determine to what extent the constrictor action of 5-hydroxytryptamine is involved in the vascular responses when it is circulating generally in the blood stream, continuous intravenous infusions of the drug were given to normal subjects and observations made of the forearm blood flow, arterial pressure, and heart rate.

METHODS

The subjects were ourselves, our colleagues, and volunteer medical students. Ages ranged from 19 to 35 years. Experiments were carried out at a laboratory temperature of $22 \pm 2°$. The subjects were lightly clothed and rested recumbent on a couch for approximately 30 min. before recordings commenced. Forearm blood flow was measured using the technique of venous occlusion plethysmography, water-filled plethysmographs (Greenfield, 1954) at 34 to 35° being applied to one or both forearms. Blood pressure was recorded by means of a capacitance manometer from a needle in the brachial artery. Saline (0.9%) was given by means of a mechanically driven syringe through a needle or a nylon catheter inserted into an antecubital vein and infused throughout the experiment at a constant rate of 4 ml./min. The saline infusion was replaced for a period of 10 min. when required by a solution of 5-hydroxytryptamine creatinine sulphate made up in 0.9% saline. Doses are expressed throughout as mg./min. of the salt. If the responses and symptoms produced by 1 mg./min. were slight or moderate in degree, a second infusion of 2 mg./min. and, in some cases, a further infusion of 3 mg./min. was given with intervals of 5 to 10 min. between infusions.

RESULTS

5-Hydroxytryptamine in a dose of 1 mg./min. was infused on 28 occasions in 25 subjects ; 14 of these also received 2 mg./min. and 9 received 3 mg./min. In all cases, forearm blood flow was measured, and in 15 experiments arterial blood pressure was recorded in addition. Pulse rates were obtained from the blood pressure record or the plethysmogram in 41 experiments. In four subjects the electrocardiogram was also recorded.

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Forearm Blood Flow. — The blood flow responses varied in different subjects. The common pattern of response is shown in the upper graph in Fig. 1. There was an initial transient increase in flow commencing within 1 to 1.5 min. of the beginning of the infusion and followed by an elevation in flow sustained through the remainder of the infusion, the flow gradually returning to the resting level over a period of 5 to 10 min. after the infusion ceased.

The transient increase in flow was present in 16 of 28 experiments with 1 mg./min.; in 10 of 14 experiments with 2 mg./min., and 8 of the 9 experiments with 3 mg./min.

The sustained increase in flow was present in 20 of the 28 experiments with 1 mg./min.; 13 of the 14 with 2 mg./min., and all 9 of those with 3 mg./min.

In three subjects there was neither a transient nor a sustained increase in flow in the forearm during the 5-hydroxytryptamine infusion. In only one of the total of 51 infusions was a fall in blood flow observed.

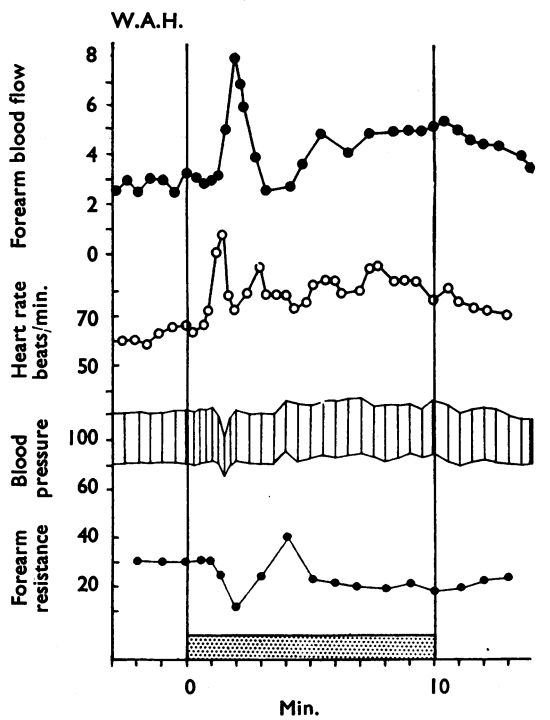

FIG. 1.—The responses of the forearm blood flow (●), heart rate (O), blood pressure, and forearm vascular resistance (•) of subject W. A. H. to 5-hydroxytryptamine creatinine sulphate administered intravenously in a dose of 2 mg./min. for 10 min. during the period indicated by the dotted area. The forearm resistance (mean pressure in mm.Hg/forearm flow in ml./100 ml./min.) is expressed in arbitrary units, blood pressure in mm. Hg, heart rate in beats/min. and forearm blood flow in ml./100 ml./min.

Nerve-Blocked Forearm.—In two experiments on two different subjects the response of the forearm blood blow to intravenous infusion (1 mg./min. of 5-hydroxytryptamine for 10 min.) was observed before and after the nerves to the forearm had been blocked by infiltration with 1% lignocaine (Whelan, 1952). The result of one of these experiments is shown in Fig. 2. The forearm flow was elevated following the nerve block as a consequence of release of vasoconstrictor tone, but the pattern of response to 5-hydroxytryptamine was not altered, and a transient, followed by a sustained, increase in flow still occurred.

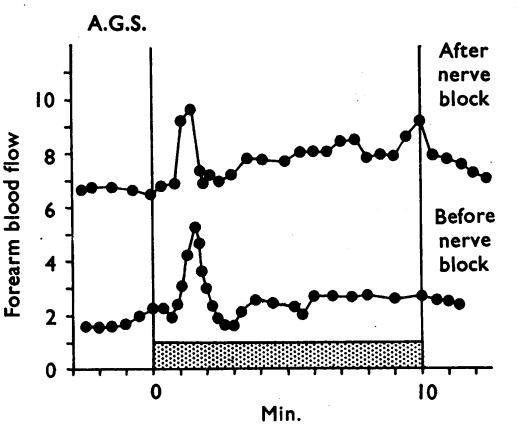

FIG. 2.—The response of the blood flow through the left forearm of subject A. G. S. to an intravenous infusion of 1 mg./min. of 5-hydroxytryptamine indicated by the dotted area before (lower curve) and after (upper curve) block of the nerves to the forearm with local anaesthetic. See legend to Fig. 1 for explanation of forearm blood flow.

Pulse Rate.—On all of the 41 occasions on which pulse rate records were obtained there was an increase during infusion of 5-hydroxytryptamine at each of the three concentrations used. The increase in heart rate commenced within 1 to 1.5 min. of the commencement of the infusion, and it invariably preceded, by 10 to 15 sec., the initial flow increase in the forearm. In 38 experiments, the pattern of the heart rate change was similar to the forearm flow changes in that there was an initial transient increase of 10 to 40 beats/min. followed by a sustained tachycardia of 5 to 30 beats/min. (Fig. 1), the larger doses having the more marked effect. In three experiments, changes in pulse rate were observed to be present but unaccompanied by any sustained increases in forearm blood flow. The results of

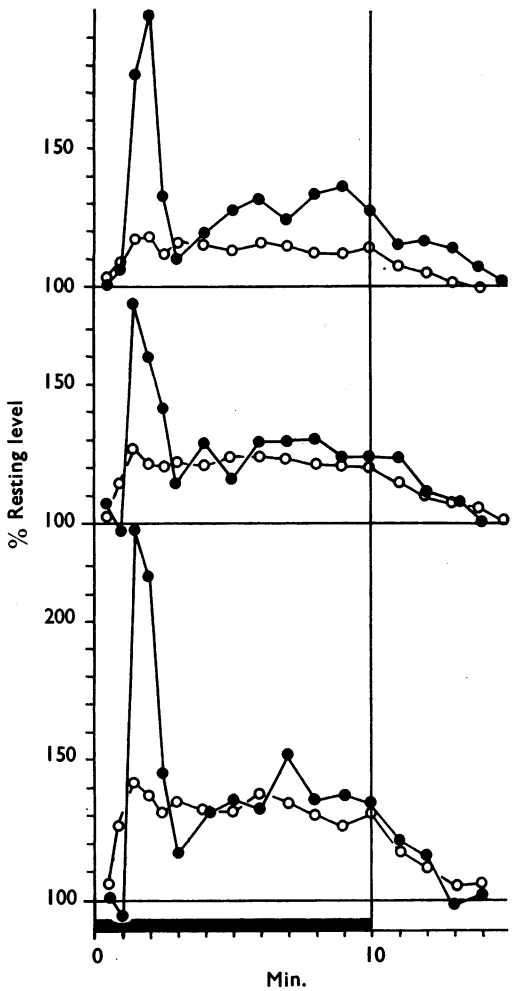

FIG. 3.—The averaged results for all experiments in which measurements of forearm blood flow and heart rate were obtained simultaneously before, during, and after intravenous infusion of 5-hydroxytryptamine indicated by the black bar. The changes in forearm flow (●) and heart rate (O) have been expressed as % of the mean of the resting values during the last 5 min. of the control period before the infusion began. Upper curves, mean of 21 experiments with a dose of 1 mg./min.; middle curves, mean of 16 experiments with a dose of 2 mg./min.; lower curves, mean of 7 experiments with a dose of 3 mg./min.

experiments in which the pulse rate and the forearm blood flow were recorded simultaneously are shown in Fig. 3.

Blood Pressure.—The blood pressure response to intravenous infusion of 5-hydroxytryptamine was variable. With 1 mg./min., in three experiments there was no change in pressure; in four there were sustained increases in mean pressure of 7, 8, 13, and 20 mm. Hg respectively. One subject showed a fall in pressure. With 2 mg./min., in three experiments there was a rise in mean pressure (6, 15, and 16 mm. Hg); in two there was no change, and in one a slight fall. With 3 mg./min. in the one experiment there was a rise in mean pressure of 13 mm. Hg.

There did not appear to be any consistent relationship between blood pressure changes and changes in forearm blood flow. In the eight subjects who showed a rise in pressure there was also an increase in flow. In five subjects there was no change in pressure, but an increase in flow occurred in four of these. Two subjects showed a fall in pressure accompanied by an increase in flow.

Electrocardiogram.—Records were obtained in seven experiments with infusions of 1, 2, and 3 mg./min. No abnormalities in conduction or rhythm were noted except a reduction in the P-R interval consistent with the tachycardia.

Signs and Symptoms.—The incidence of symptoms was found to increase with increasing doses of 5-hydroxytryptamine. Thus in only 12 of 28 experiments with 1 mg./min. were symptoms noted, while with 2 mg./min. 13 of 14 noticed symptoms and with 3 mg./min. all subjects were affected. The symptoms, in descending order of frequency of occurrence, were: pain along the course of the infused vein; heaviness in the legs and arms; pressure in the head and eyes; nausea; awareness of increased respiration; abdominal cramps; tightness in the chest. Miscellaneous symptoms which were occasionally noted were pulsation of arteries, blurred vision, sweating, excessive salivation, headache, lightness in the head, and an abnormal sense of smell. Signs noted by the observers included a malar flush and sometimes a flush of the neck occurring 2 to 3 min. after the beginning of the infusion. Erythema and tenderness along the course of the infused vein commonly occurred and often extended into the axilla. No flushing of the forearm or hand skin was apparent at any of the doses used.

The incidence of thrombosis appeared to be abnormally high in the veins infused with solutions of 5-hydroxytryptamine. In some cases this was noted at the end of the experiment, while in others on the following day the vein was found to be tender, thickened, and cord-like.

Abnormal Responses.—In two subjects the responses to intravenous 5-hydroxytryptamine were sufficiently different from the usual to warrant separate description. In the first of these (Fig. 4) forearm blood flow and brachial arterial

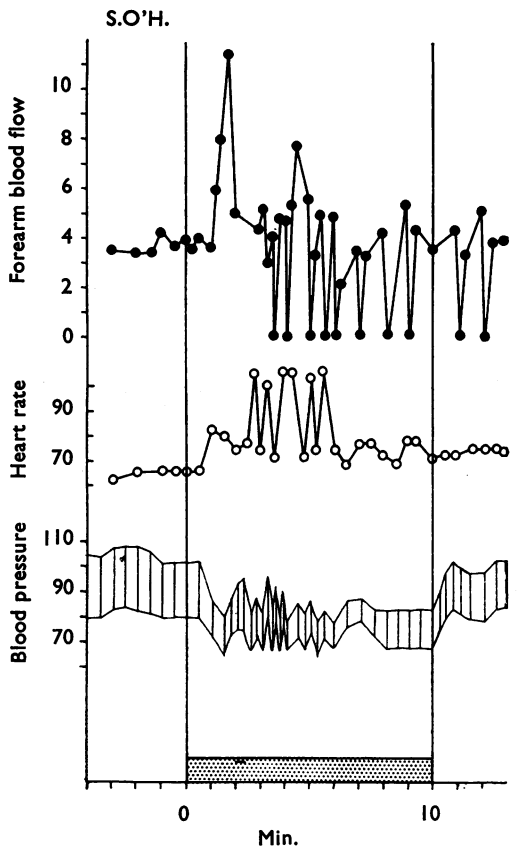

FIG. 4.—The changes in forearm blood flow (●), heart rate (O) and blood pressure in subject S. O'H. during intravenous infusion of 1 mg./min. of 5-hydroxytryptamine for 10 min. indicated by the dotted area. For explanation of ordinates, see legend to Fig. 1.

blood pressure were measured. In the first 3 min. of a 10 min. infusion of 5-hydroxytryptamine at a dose of 1 mg./min., an initial transient increase in blood flow occurred, preceded 15 to 20 sec. earlier by a rise in heart rate from 65 to 80 beats/min., and accompanied by a fall in blood pressure from the pre-infusion level of 105/80 to 80/65 mm. Hg. For the remaining 8 min. of the infusion, the blood pressure, the heart rate, and the blood flow showed a series of marked oscillations. The peaks in the blood pressure never rose above 100 mm. Hg systolic. On cessation of the infusion, the blood pressure and heart rate returned to normal levels within 1 to 2 min. though the forearm flow continued to show fluctuations. The subject had no symptoms during or after the infusion. Seven weeks later he submitted to a second infusion of the same dose. Within 2 min. of the onset of the infusion, the blood pressure fell to 75/35 mm. Hg, the heart rate rose from 72 to 100 beats/min., and the forearm flow increased fourfold. Symptoms of nausea and palpitation were present and the infusion was stopped after 1.75 min., following which the pressure and heart rate returned to normal over a period of 5 min. An electrocardiogram was taken throughout, and this showed, in addition to a shortening of the P-R interval associated with tachycardia, two isolated instances of inversion of the P wave, one just before the end of the infusion and one just after.

The second subject received 1 mg./min. of 5-hydroxytryptamine for a period of 30 min., while the forearm blood flow was being measured. The usual transient increase in flow occurred followed by a moderate sustained increase in flow. In the last 3 min. of the infusion the forearm flow rose markedly and the subject complained of nausea, pounding in the head and legs, and showed sweating and a marked pallor. The infusion was discontinued and the effects passed off over 5 min. Four weeks later a second infusion of 1 mg./min. was given to this subject. This had to be terminated at the end of 1.5 min. because of the marked symptoms of nausea, headache, dyspnoea, shivering, and sweating which developed. Recovery occurred within 5 to 10 min. of stopping the infusion.

DISCUSSION

The direct action of 5-hydroxytryptamine on the blood vessels of the limbs in man has been shown to be a complex one. When it is infused into the brachial artery at a constant rate of 1 to 16 μg./min. the blood flow through the forearm, after an initial transient dilatation, is reduced, indicating a constriction of arterioles (Roddie *et al.*, 1955); the capacity vessels, probably mainly the veins and venules, show an increase in their tone (Glover, Greenfield, Kidd, and Whelan, 1958); the capillaries are dilated as evidenced by the flushing of the skin, and, with larger doses, there is an increase in limb volume suggesting an increased capillary permeability and oedema formation (Roddie *et al.*, 1955).

The results of the present experiments demonstrate that, when 5-hydroxytryptamine was given by the intravenous route so that a concentration comparable to the intra-arterial doses mentioned above circulated generally through the body, an initial transient 3- to 4-fold increase in forearm blood flow was still seen but the subsequent vasoconstriction did not occur, being replaced in the majority of cases by an increased flow of 20 to 30% above the resting

level. This suggests that when 5-hydroxytryptamine is given intravenously some secondary dilator mechanism is in force to oppose the direct constrictor action of the drug.

The averaged results for simultaneous blood flow and heart rate measurements shown in Fig. 3 demonstrate that the heart rate response increases with increasing doses of 5-hydroxytryptamine. Such a relation was not apparent in the case of the sustained effect on forearm blood flow, which supports the suggestion that the forearm response is a resultant of two opposing effects, an indirect dilator action being countered by a direct constrictor action. If both of these effects were equally enhanced by increased doses, the balance could be maintained almost constant at the different doses.

That the dilator action is not mediated by way of the sympathetic nerves as the result of some central or reflex effect of 5-hydroxytryptamine is shown by the fact that the dilator response was not modified by blocking the nerves to the forearm.

The dilator action may in part be a result of a raised perfusion pressure in the limb as a consequence of a raised blood pressure, but is unlikely to be wholly accounted for in this way since the rise in pressure, when it occurred, was not great and was probably insufficient to account for the accompanying increase in forearm flow if a direct pressure/flow relationship was assumed. Furthermore, an increase in forearm blood flow has been observed in a number of experiments in which the blood pressure had fallen or remained unchanged.

The response of the forearm flow is in many respects similar to that seen during intravenous infusion of adrenaline (Allen, Barcroft, and Edholm, 1946) although the sustained dilatation was usually less marked than with adrenaline. It has been shown by Reid and Rand (1951) that 5-hydroxytryptamine can release adrenaline from the adrenal medulla, and it is possible that the vascular effects of 5-hydroxytryptamine in man may in part be a consequence of release of adrenaline.

The pattern of the heart rate changes is also similar to that seen with adrenaline. However, in the present experiments the rapid onset of the tachycardia after the beginning of the infusion and the fact that it invariably preceded the changes in forearm flow and blood pressure suggest that the tachycardia was caused by the direct action of 5-hydroxytryptamine on the heart and not as a consequence of adrenaline release nor of any haemodynamic reflexes due to changes in peripheral resistance. This is further supported by the fact that tachycardia was seen in a number of experiments with doses of 5-hydroxytryptamine which had no effect on the blood pressure or peripheral flow.

The abnormal responses seen in two of the subjects were suggestive of a hypersensitivity to 5-hydroxytryptamine, particularly in view of the repetition of the effects on the second infusion some weeks later. No corresponding reports of this nature have been found in the literature available to us. As a consequence of these findings, it was considered advisable in all subsequent experiments to carry out an infusion of 1 mg./min. for at least 5 min. as a preliminary to the administration of any larger dose.

The high incidence of venous thrombosis observed in this series after intravenous infusions, the pain and tenderness along the course of the vein, and the redness of the overlying skin are evidence of the local irritant properties of 5-hydroxytryptamine.

No flushing of the forearm or hand skin was apparent at any of the dose levels, and, while it was not possible to state whether the forearm vasodilatation originated in the muscles or the skin vessels, or both, it seems unlikely that it could wholly be accounted for by dilatation of skin vessels.

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