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ANTAGONISM BY METHYSERGIDE OF VASCULAR EFFECTS OF 5-HYDROXYTRYPTAMINE IN MAN

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The vascular responses in the upper limbs of normal human subjects to intra-arterially administered 5-hydroxytryptamine (5HT) were described by Roddie, Shepherd & Whelan (1955) and by Bock, Dengler, Khun & Matthes (1957). Glover, Marshall & Whelan (1957) found the lysergic acid derivative 2-bromo-(+)-lysergic acid diethylamide bitartrate (BOL 148) to be a specific antagonist of the constrictor response of forearm and hand blood vessels to intra-arterial infusions of 5-HT.

Methysergide has been used therapeutically in the long term management of migrainous headaches in the pathogenesis of which 5-HT may be involved (Ekbom, 1962; Friedman & Elkind, 1963; Curran & Lance, 1964; Graham, 1964). Its effectiveness in reducing diarrhoea in patients suffering from the carcinoid syndrome has been reported by Peart & Robertson (1961), Melmon, Sjoerdsma, Oates & Laster (1965) and Mengel (1965). The possible use of methysergide in the management of post-gastrectomy syndromes and post-vagotomy diarrhoea has been indicated by Peskin & Miller (1965).

The present study was undertaken to determine the effects of methysergide on the responses of limb blood vessels to infused 5-HT and other vasoactive substances in normal subjects and also to investigate the specificity of 5-HT receptors in blood vessels.

METHODS

The subjects were colleagues and volunteer medical and physiotherapy students (ages 18–28 yr) and two patients who had undergone cervical sympathectomy (ages 31 and 37 yr). They lay supine on a couch in a temperature-controlled laboratory (22–24° C) for at least 30–40 min before observations began, during which time the recording apparatus was applied and needles or catheters inserted.

Blood flow through the hands was recorded using the water-filled temperature-controlled plethysmographs described by Greenfield (1954), the plethysmograph temperature being maintained at 32° C. The volume change was recorded by means of float recorders on a kymograph drum.

Forearm blood flow was measured with capacitance plethysmographs (Willoughby, 1965; Fewings & Whelan, 1966). The plethysmograph consisted of a shielded copper cylinder, formed to the shape of the forearm and separated from it by a mean spacing of 1.25 ± 0.25 cm. The copper cylinder constituted one plate of a capacitor system. The second plate, the surface of the arm, was earthed to the shielding screen by shim brass surface electrodes at the wrist and upper arm. A

constant current at a fixed frequency was passed across the capacitor. The volume change caused by venous occlusion produced an increase in capacity and a decrease in output voltage. The voltage was rectified, amplified and fed to a rectilinear pen-writer system (Oscilloriter, Model 323B medium) frequency recorder, Texas Instruments, Inc.).

In three subjects the effects of 5-HT and methysergide on the vessels of the skin and muscle of the forearm were followed independently by determining the changes (%) in haemoglobin saturation with oxygen of samples of blood taken from catheters inserted into a superficial and a deep forearm vein respectively (Roddie, Shepherd & Whelan, 1956, 1957).

Changes in the reaction of the capacity vessels of the hand and forearm were studied, each in one subject, using the method described by Glover, Greenfield, Kidd & Whelan (1958). The hand or forearm was enclosed in a water-filled plethysmograph and venous congestion was produced by inflating a pneumatic cuff applied to the limb just proximal to the plethysmograph. Increases in the volume of the part displaced water from the plethysmograph into a burette calibrated in millilitres. The position of the burette was continuously adjusted to keep the meniscus at a level 10 cm above the centre of the limb segment, and the burette reading was noted at 30 sec intervals. Venous congestion pressures of 20, 40 or 60 mm Hg were applied and each was maintained until the rate of increase of volume of the part fell below 0.15 ml./100 ml. of tissue/min, usually a period of 3–4 min. The pressure was then returned to atmospheric and the limb volume allowed to stabilize at the resting level before further measurements were made, usually 2–3 min.

A wrist cuff was inflated to 200 mm Hg during measurements of forearm blood flow and venous capacity in order to exclude the hand circulation.

Intra-arterial infusions of drugs were administered through a 22-gauge needle inserted under local anaesthesia (lignocaine 2%) into the brachial artery in the cubital fossa. The needle was connected by a 30 cm length of 0.5 mm bore polyethylene tubing to a mechanically-driven syringe. Saline (0.9% W/V) was infused continuously at a rate of 2 ml./min throughout the experiment and was used as a vehicle for the drugs. Observations were made on both limbs simultaneously, three or four flow records being taken each minute. Following a control period of flow measurements of 3 to 5 min an infusion of a drug was administered to one side through the intra-arterial needle and flow measured on both sides until 3 to 5 min after the end of the drug infusion. Calculation of % age change in blood flow during intra-arterial infusion of 5-HT was made by obtaining the average of blood flow measurements taken during the 2 min immediately before the infusion and comparing it with the average flow during the last 2 min of the infusion. Where appropriate, correction for spontaneous changes in the blood flow was made by reference to the control side (Duff, 1952). The drugs used were acetylcholine chloride (Roche), adenosine triphosphate (Light), adrenaline hydrochloride (D.H.A.), angiotensin II (val^5-hypertensin II-asp-β-amide, Hypertensin CIBA), bradykinin (BRS 640, Sandoz), histamine acid phosphate (B.D.H.), hyoscine hydrobromide (Farmer Hill), methysergide (1-methyl-d-lysergic acid butanolamide bimaleate, UML 491, Deseril, Sandoz), noradrenaline bitartrate monohydrate (Levophed, Winthrop), phenoxybenzamine hydrochloride (Dibenyline, S.K.F.), propranolol (Inderal, I.C.I.) and 5-hydroxytryptamine creatinine sulphate (5HT, SR 134, Sandoz). Doses are expressed as weights of the salts. Ascorbic acid (1:50,000) was added to the adrenaline and noradrenaline solutions.

RESULTS

Forearm blood flow

In 8 subjects infusions of 5-HT of 2, 4, 8 μg/min and in one subject 16 μg/min for 5 min were given into one brachial artery and the blood flow measured on both sides.

5-HT caused an initial transient dilatation followed by a sustained fall in flow, the latter fall being dose dependent. Red flushing of forearm skin was observed and prickling sensations were often experienced. These changes were similar to those described by Roddie *et al.* (1955). The infused arm was then treated with methysergide (25 μg/min for 10 min) and doses of 5-HT were repeated. The initial dilatation was not

consistently or greatly altered by methysergide administration but the subsequent vasoconstriction was abolished or converted to a slight dilatation, as shown in Fig. 1. Similar results were obtained in each of the 8 subjects (Table 1).

The above dose of methysergide was effective for at least 20 min since repeated infusions of 5-HT produced no vasoconstriction until 25 min after the end of the methy-

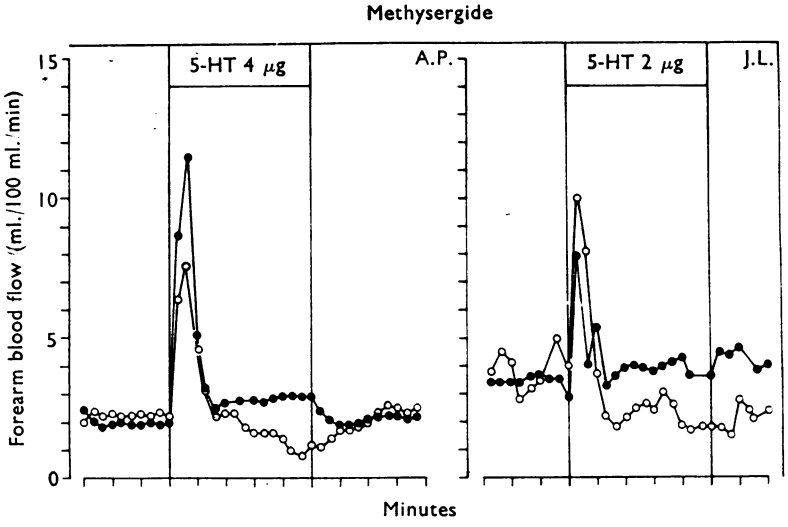

Fig. 1. The effect of intra-arterial infusions of 5-HT (5HT, 4 and 2 μg/min) on blood flow through the forearm before (○) and after (●) intra-arterial infusion of methysergide (25 μg/min for 10 min) in 2 subjects. Blood flow in ml./100 ml./min.

TABLE 1

THE % CHANGES IN BLOOD FLOW IN THE HANDS AND FOREARMS DURING INTRA-ARTERIAL INFUSION OF 5-HT BEFORE AND AFTER INTRA-ARTERIAL INFUSION OF METHYSERGIDE, 25 μG/MIN FOR 10 MIN

The minus and plus signs represent decreases and increases in flow respectively.

	Dose of intra-arterial 5-HT							
Forearms	2 μg/min		4 μg/min		8 μg/min		16 μg/min	
Subject	Before	After	Before	After	Before	After	Before	After
L.A.	—	—	−61·0	−12·0	−56·0	−20·0	—	—
S.S.	—	—	—	—	−50·0	−6·3	−71·4	−18·0
V.H.	−13·6	−4·0	−4·6	−18·1	−37·5	−4·5	—	—
D.R.	+28·2	+62·2	—	—	−53·7	+28·2	—	—
J.L.	−58·0	+18·3	—	—	−69·2	−25·0	—	—
B.T.	—	—	—	—	−33·3	+27·3	—	—
H.C.	—	—	−11·7	+13·3	—	—	—	—
A.P.	—	—	−40·9	+52·6	—	—	—	—
Average	−14·3	+25·5	−29·5	+8·9	−49·9	−0·08	−71·4	−18·0
Hands								
O.C.	—	—	—	—	−1·1	+30·2	−58·2	+25·0
J.D.	—	—	—	—	−46·1	−23·2	—	—
M.L.	—	—	—	—	—	—	−30·0	+6·1
W.C.	—	—	—	—	—	—	−65·0	−12·3
J.R.	—	—	—	—	−54·2	+13·0	—	—
D.C.	—	—	—	—	—	—	−63·3	+25·0
Average	—	—	—	—	−37·1	+6·6	−54·1	+10·9

sergide infusion. An additional infusion of methysergide (25 μg/min for 5 min) was given when 20 min had elapsed. Methysergide itself produced no change in blood flow with the above dose.

In three subjects superficial and deep forearm venous blood oxygen saturation estimations were made during intra-arterial infusion of 5-HT before and after treatment with methysergide. These indicated that the modification of the total forearm response to 5-HT by methysergide (Fig. 1) was due to an abolition of the vasoconstriction in skin and an enhanced vasodilator response of muscle vessels, as the oxygen saturation of superficial samples did not fall and that of the deep samples showed a more sustained elevation during the 5-HT infusion subsequent to methysergide treatment. Figure 2 illustrates the results of one of these experiments.

Intravenous 5-HT (1 mg/min for 8 min) was administered to 2 subjects *via* a polyethylene catheter (Intracath, Bardic) before and after intra-arterial infusion of methysergide (25 μg/min for 10 min) to one forearm. The normal vasodilator response

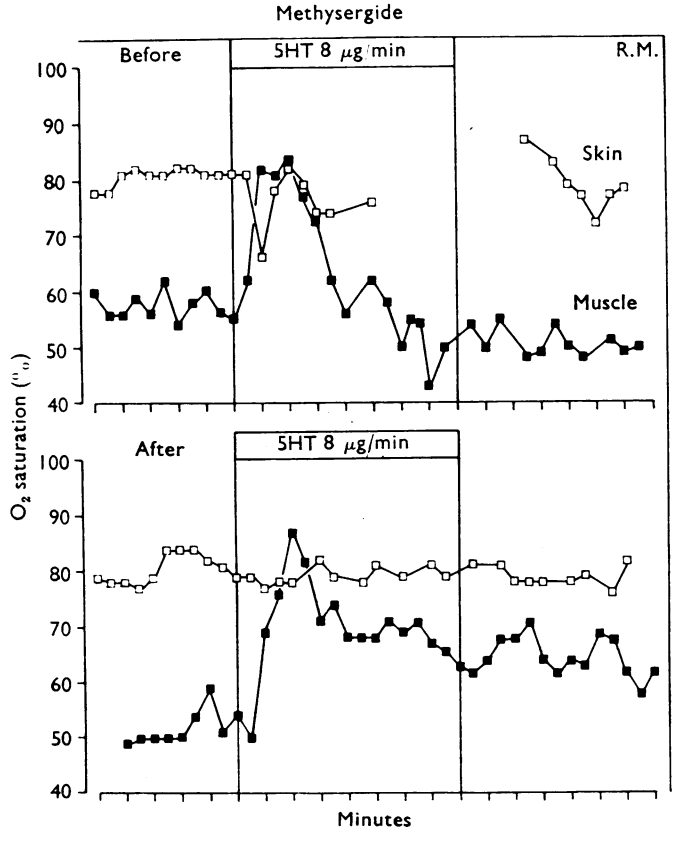

Fig. 2. The effect of intra-arterial infusion of 5-HT (5HT, 8 μg/min for 8 min) on the % oxygen saturation of blood samples taken from veins which drained the skin (□) and muscle (■) of the same forearm before (upper frame) and after (lower frame) intra-arterial infusion of methysergide (25 μg/min for 10 min).

of the forearm to 5-HT infused intravenously (LeMessurier, Schwartz & Whelan, 1959) was enhanced in the forearm pretreated with methysergide in each subject.

Hand blood flow

The effect of methysergide on the response of the hand vessels to intra-arterial 5-HT (8 or 16 μg/min for 5 min) was studied in six subjects (Table 1). The normal vasoconstrictor response (Roddie *et al.*, 1955) was replaced by a significant dilatation in 4 subjects (as in O.C., Fig. 3) and greatly reduced in 2 subjects (as in J.R., Fig. 3).

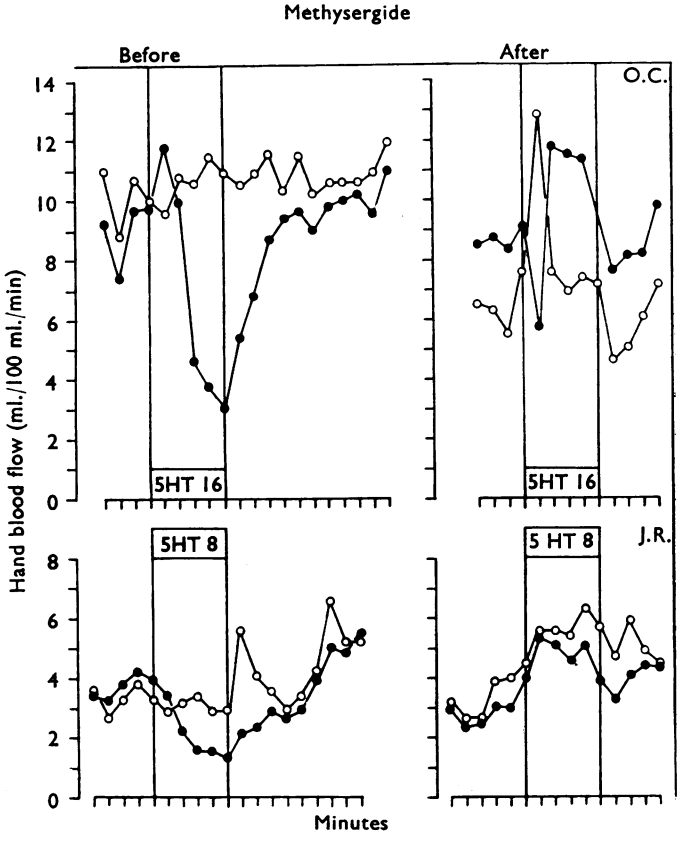

Fig. 3. The effect of intra-arterial infusion of 5-HT (5HT, 16 and 8 μg/min) on the blood flow through the hand (ml./100 ml./min) before (left hand frames) and after (right hand frames) intra-arterial infusion of methysergide (25 μg/min for 10 min) in 2 subjects. ●, infused side; ○, control side.

Figure 4 summarizes the results of 7 infusions on the above 6 subjects (hand blood flow) and 14 infusions on the 8 subjects in whom forearm flow was measured before and after methysergide 250 μg. In all cases there was antagonism of the vasoconstrictor action of 5-HT and in most cases a vasodilatation occurred, the dilatation being more marked with the smaller doses of 5-HT.

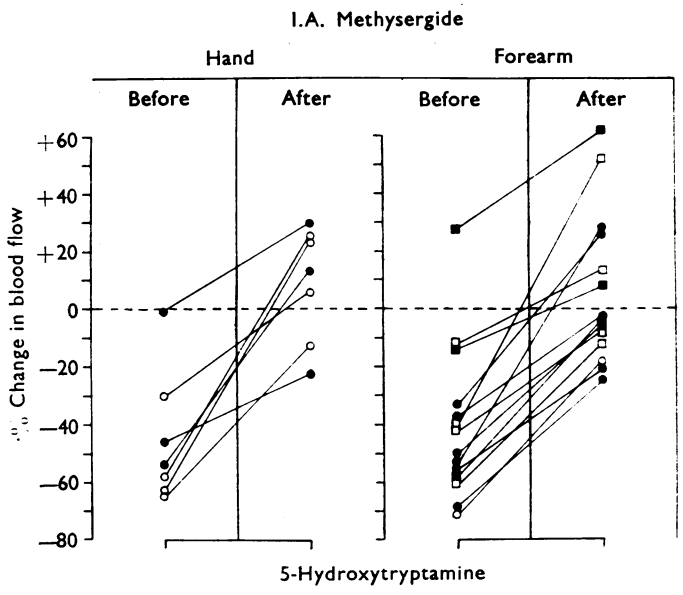

Fig. 4. The pooled data from 14 normal subjects of the % changes in blood flow through the hand (left-hand frame) and forearm (right-hand frame) resulting from intra-arterial infusions of 5-HT before and after intra-arterial infusion of methysergide (25 μg/min for 10 min). Dose of 5-HT (μg/min): ■, 2 ; □, 4 ; ●, 8 ; ○, 16.

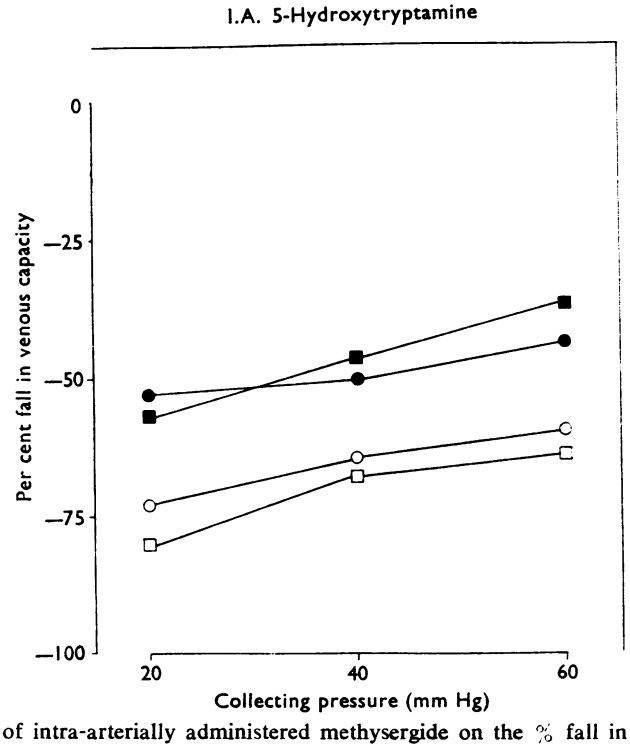

Fig. 5. The effect of intra-arterially administered methysergide on the % fall in venous capacity of the vessels of the upper limb resulting from intra-arterial infusion of 5-HT (4 μg/min continuously) in 2 subjects. □, before ; ■, after methysergide 300 μg (hand). ○, before ; ●, after methysergide 500 μg (forearm). Venous collecting pressures: 20, 40, 60 mm Hg.

Venous capacity

Administration of 5-HT intra-arterially (4 μg/min continuously) produced a reduction in venous capacity of the vessels of the hand (one subject) and forearm (one subject). This potent venoconstrictor action of 5-HT was partially antagonized by methysergide, 300 μg and 500 μg respectively (Fig. 5).

Flush

Methysergide abolished the skin flushing which occurred during the control infusions of 5-HT.

Specificity of the action of methysergide

The effect of methysergide on responses of upper limb vessels to other vasoactive substances administered intra-arterially was studied in many of the above subjects. The fall in hand blood flow which occurs with noradrenaline and adrenaline (0.2 μg/min for 4 min) was studied before and after methysergide in 2 subjects. The vasoconstrictor action of the catecholamines was unaffected by methysergide, whereas the vasoconstrictor effect of 5-HT was converted to a dilatation. Figure 6 shows the result of one of these experiments.

The responses of the forearm vessels to adrenaline (0.1–0.4 μg/min for 4 min; 4 subjects), histamine (0.5–5.0 μg/min for 3 min; 3 subjects), acetylcholine (2.5 μg/min for

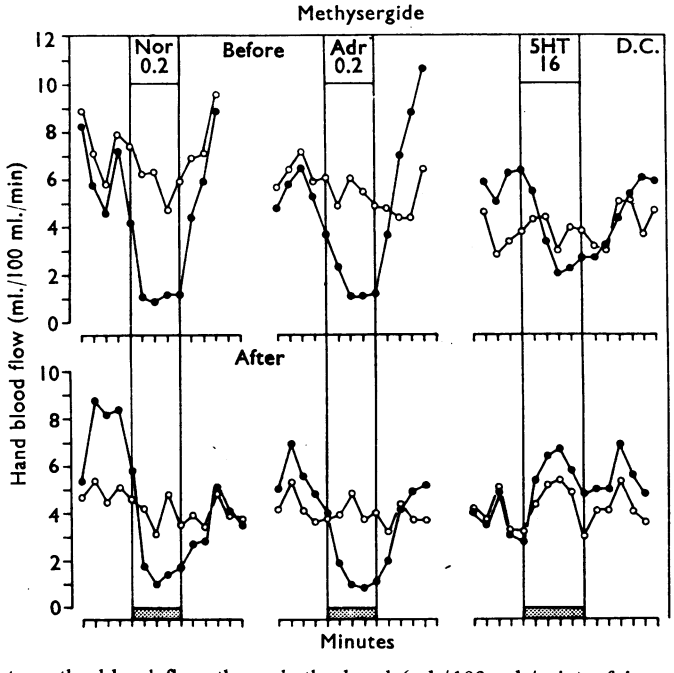

Fig. 6. The effect on the blood flow through the hand (ml./100 ml./min) of intra-arterial infusions of noradrenaline and adrenaline (0.2 μg/min for 4 min) and 5-HT (5HT, 16 μg/min for 5 min) before (upper frames) and after (lower frames) intra-arterial infusion of methysergide (25 μg/min for 10 min). ●, infused side; ○, control side.

3 min; 2 subjects), bradykinin (0.05 μg/min for 1 min; one subject) and adenosine triphosphate (50 μg/min for 2 min; one subject) were unchanged by adminstration of methysergide. Typical examples are shown in Fig. 7. Similarly, there was no change in the response of the forearm vessels to the vasoconstrictor drugs noradrenaline (0.05 μg/min for 4 min; 2 subjects) and angiotensin (0.004 μg/min for 4 min; one subject). These results indicate that methysergide is a specific antagonist of peripheral vasoconstrictor effects of 5-HT.

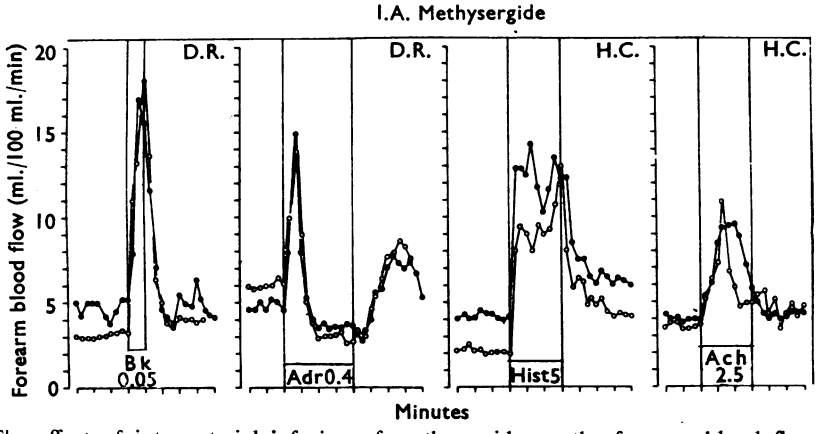

Fig. 7. The effect of intra-arterial infusion of methysergide on the forearm blood flow responses (ml./100 ml./min) to intra-arterial infusions of bradykinin (Bk 0.05 μg/min), adrenaline (Adr 0.4 μg/min), histamine (Hist 5 μg/min) and acetylcholine (Ach 2.5 μg/min) in 2 subjects (D.R. and H.C.). ○, before; ●, after methysergide (25 μg/min for 10 min).

Specificity of 5-HT receptors

Phenoxybenzamine. The α-receptor blocking drug phenoxybenzamine (250 μg/min for 8 min) was administered to 3 subjects after control infusions of adrenaline and 5-HT to the hand (2 subjects) and forearm (one subject). Figure 8 (upper frame) shows abolition of the adrenaline-induced vasoconstriction in one subject after treatment of the hand with phenoxybenzamine but persistence of the fall in hand blood flow caused by 5-HT. Similarly, phenoxybenzamine abolished the vasoconstrictor effect of adrenaline on the forearm and produced a pronounced dilatation, whereas the pattern of response to 5-HT was essentially unchanged although the resting flow increased due to release of vessel tone by the phenoxybenzamine (Fig. 8, lower frame).

Propranolol. Intra-arterial infusion of the β-receptor blocking agent propranolol (0.1 mg/min for 5 min) was administered to 3 subjects after control responses to adrenaline and 5-HT had been recorded. The responses to 5-HT were not substantially modified whereas adrenaline now produced vasoconstriction only, the dilator effects being completely abolished (Fig. 9, upper frame).

Hyoscine. Intra-arterial infusion of the post-ganglionic acetylcholine receptor blocking agent hyoscine (0.1 mg/min for 4 min: 2 subjects) did not alter the response of the forearm vessels to 5-HT (4 μg/min), whereas the dilator effect of acetylcholine (5 μg/min)

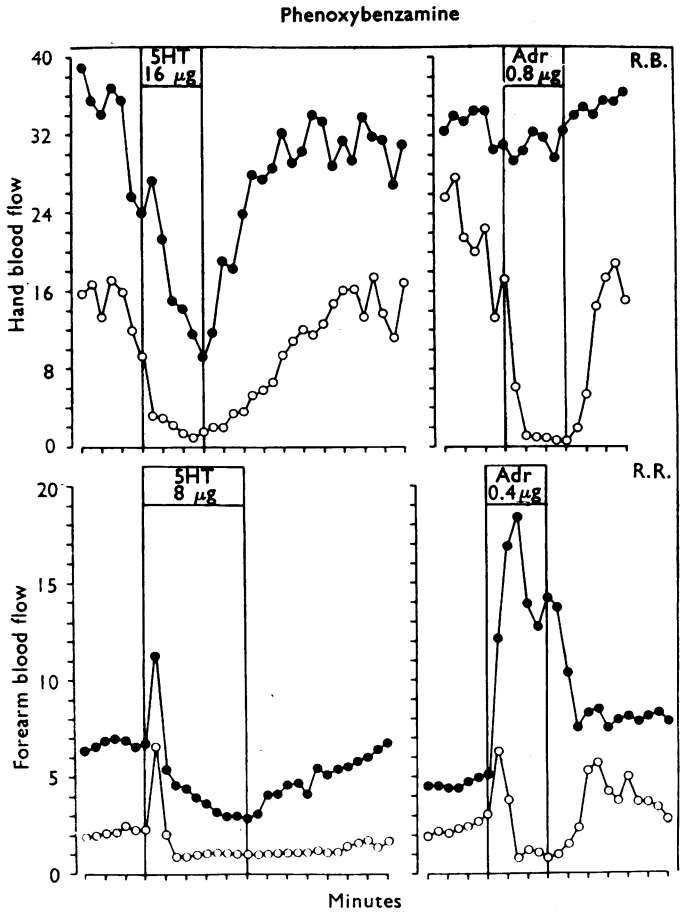

Fig. 8. The effect of intra-arterial infusion of 5-HT (5HT 16 and 8 μg/min) and adrenaline (Adr 0.8 and 0.4 μg/min) on the blood flow through the hand (upper frames) and forearm (lower frames) before (○) and after (●) intra-arterial infusion of phenoxybenzamine (250 μg/min for 8 min) in 2 subjects. Blood flow in ml./100 ml./min.

was completely abolished. Figure 9 (lower frame) shows the result of one of these two experiments.

5-HT and sympathetic innervation. The influence of sympathetic innervation on the vasoconstrictor action of serotonin on the hand was investigated in four experiments. Intra-arterial 5-HT (2 and 4 μg/min for 5 min) was administered before and after the intra-arterial administration of the sympathetic nerve-blocking agent bretylium (4 mg/min for 5 min) in 2 subjects. The effect of 5-HT was unchanged. The effectiveness of the bretylium-induced sympathetic nerve block was demonstrated by abolition of the sympathetic constrictor reflex response of hand vessels to the stimulus of ice applied to the neck (Cooper, Fewings, Hodge & Whelan, 1963). This independence of 5-HT of the autonomic nerve supply was confirmed by the observation of normal responses of

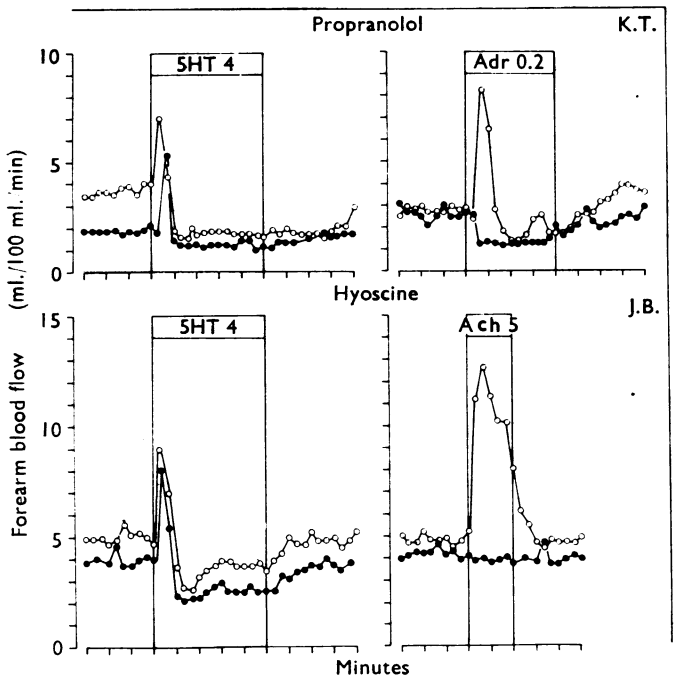

Fig. 9. Upper frame (K.T.). The response of the forearm blood flow to intra-arterial infusion of 5-HT (5HT, 4 μg/min) and adrenaline (Adr, 0.2 μg/min) before (○) and after (●) intra-arterial infusion of propranolol (0.1 mgm/min for 5 min). Lower frame (J.B.). The response of the forearm blood flow to intra-arterial infusion of 5-HT (5HT, 4 μg/min) and acetylcholine (Ach, 5 μg/min) before (○) and after (●) intra-arterial infusion of hyoscine (0.1 mgm/min for 4 min). Blood flow in ml./100 ml./min.

the hand vessels to intra-arterial 5-HT in 2 patients who had undergone cervical sympathectomy many months previously and in whom all sympathetic nerve activity was absent as evidenced by lack of reflex sympathetic responses and loss of vasoconstriction to intra-arterial ephedrine (Parks, Skinner & Whelan, 1961).

DISCUSSION

The antagonism by methysergide of vasoconstrictor effects of 5-HT on the vessels of the hand and forearm in man is of the same nature as the antagonism by BOL 148 described by Glover *et al.* (1957). Lysergic acid and its derivatives, including BOL 148, have been shown to antagonize the effects of 5-HT on isolated smooth muscle preparations (Gaddum & Hameed, 1954). Similarly, this more recent lysergic acid derivative, methysergide, has been found to be an effective antagonist of 5-HT on animal preparations. Doepfner & Cerletti (1958) showed that methysergide has four to six times the potency of lysergic acid in antagonizing 5-HT-provoked oedema in the rat's paw.

Using the technique of superficial and deep oxygen saturation estimations to follow changes in skin and muscle blood flow, Whelan (1967) showed that intra-arterial infusion of 5-HT to the forearm caused a fall in the oxygen saturation of blood draining from

skin and a rise in that of blood draining from muscle. Assuming that the oxygen consumption of the tissues remains constant, then a fall in oxygen saturation of the sampled blood denotes a decrease in blood flow and a rise in saturation an increase. Thus the total forearm flow changes with infused 5-HT were considered to be a resultant of vasoconstriction in skin and vasodilatation in muscle. A similar conclusion was reached by Bock *et al.* (1957) who measured skin blood flow with a heat flow calorimeter and muscle blood flow with a Hensel needle. This observation that 5-HT, although a constrictor of the hand vessels and those of the skin of the forearm, is a dilator of the vessels of the underlying muscle, is in accord with the suggestion of Fox, Goldsmith, Kidd & Lewis (1961) and accounts for the fact that, when the skin flow is high, 5-HT causes a fall in total forearm flow due to the predominant effect of the skin vessel constriction, whereas when the skin flow is low an increase in forearm flow may be seen due to the muscle dilatation being more manifest. These opposite effects of 5-HT on skin and muscle vessels resemble closely those of adrenaline. That there is a marked constrictor component to 5-HT's action on muscle vessels is demonstrated by the fact that after antagonism of the constrictor effect by methysergide a greater and more sustained dilatation of muscle vessels occurred. It would appear that skin vessels have constrictor receptors to 5-HT while the underlying muscle vessels have both constrictor and dilator receptors, the action on the latter normally predominating.

As with BOL 148 the antagonism by methysergide is not a consequence of a non-specific inhibition of smooth muscle since the ability of the vessels to respond to other vasoactive drugs, both dilator and constrictor, was unaffected. Methysergide was, therefore, considered to be a specific and effective antagonist of peripheral vasoconstrictor effects of 5-HT. Although it is difficult to extrapolate drug actions from one vascular bed to another this action of methysergide may contribute to its effectiveness in preventing migraine, the prodromal stage of which is associated with vasoconstriction of extracranial and intracranial arteries, an action ascribed in part to 5-HT (Sicuteri, 1959).

The effect of methysergide in opposing the potent venoconstrictor action of 5-HT was observed in two experiments. This anti-venoconstrictor effect may explain the abolition of the skin flush which normally occurs during intra-arterial infusion of 5-HT since Oyvin & Shegal (1965) attribute the 5-HT flush to hyperaemia of stasis, a consequence of constriction of large veins plus small vessel dilatation and oedema formation, and Haddy, Fleishman & Emanuel (1957) have found that intra-arterial 5-HT increases large vein resistance and decreases small vein resistance in the dog's forelimb.

McCubbin, Kaneko & Page (1962) suggested that catecholamine dilator receptors mediate the ability of 5-HT to oppose neurogenic vasoconstriction in the perfused hind-limb of the anaesthetized dog. However, the β-receptor blocking agent propranolol did not affect the pattern of response of the human forelimb to infused 5-HT. Similarly, the α-receptor blocking drug phenoxybenzamine did not block 5-HT-induced vasoconstriction. Both blocking agents were effective antagonists of infusions of adrenaline in the same experiments.

The acetylcholine receptor blocking agent hyoscine did not modify the effect of 5-HT on the forearm indicating that its dilator action is independent of the acetylcholine vasodilator receptors.

Acute blockade of the sympathetic nerve supply to the hand by bretylium and chronic cervical sympathectomy with degeneration of sympathetic nerves did not modify the effects of intra-arterially administered 5-HT.

It is concluded that in the case of the vessels of the upper limb in man 5-HT acts upon specific receptors which are independent of the catecholamine and acetylcholine receptors and also of sympathetic innervation.

SUMMARY

1. 5-HT infused into the brachial artery in man caused vasoconstriction in skin and vasodilatation in muscle, the latter masking a muscle vasoconstrictor action.

2. Intra-arterial methysergide specifically antagonized the vasoconstrictor effects of 5-HT on skin and muscle of the upper limb in man.

3. Methysergide antagonized the 5-HT-induced venoconstriction and skin flush.

4. The peripheral effects of 5-HT on the upper limb were independent of the catecolamine and acetylcholine receptors and of sympathetic innervation.

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