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THE ACTION OF NICOTINE ON THE BLOOD VESSELS OF THE HAND AND FOREARM IN MAN

BY

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In most studies of the action of nicotine on the blood vessels in man, intravenous injections have been used. Nicotine has been reported to reduce the circulation through the skin (Maddock & Coller, 1933; Johnston, 1942; Roth, McDonald & Sheard, 1944; Rottenstein, Peirce, Russ, Felder & Montgomery, 1959), and to increase forearm venous tone (Eckstein & Horsley, 1960) and muscle blood flow (Rottenstein *et al.*, 1959, 1960). These effects were accompanied by tachycardia, nausea and pallor and an increase in blood pressure. It is not possible to determine whether the limb vessel responses were caused by actions of nicotine on the central nervous system or on sympathetic nerves, or to a direct action on the vessels. Strömblad (1959) gave intra-arterial infusions of nicotine into the brachial artery in man and reported a vasoconstriction in the hand which was abolished by dihydroergotamine and dibenamine. Skinner & Whelan (unpublished) found that intra-arterial nicotine caused dilatation of the vessels of the human forearm.

This paper describes the effects of intra-arterial injections of nicotine on the vessels of the forearm and hand in human subjects. The responses were found to contain both constrictor and dilator components and the mechanisms of these have been investigated.

METHODS

The subjects in most experiments were healthy males who lay supine on a couch in a temperature-controlled laboratory (23 to 25° C) for at least 30 min before observations began. Water-filled, temperature-controlled plethysmographs (Greenfield, 1954) were used to measure the blood flow through the hands, and capacitance plethysmographs (Fewings & Whelan, 1966) to measure the blood flow through the forearms. The circulation through the hand was arrested by a pneumatic cuff inflated to 200 mm Hg during the measurement of forearm flow.

Drugs were introduced into the brachial artery in the cubital fossa of one arm through a 22-gauge short-bevel needle attached by a 30 cm length of polyethylene tubing to a mechanically driven syringe which delivered 2 ml. of solution per min. Saline (0.9%, w/v) was infused during control periods and was used as a vehicle for the drugs.

Nicotine hydrogen tartrate (Stimuline; Woods, Australia) was administered intra-arterially by introducing the solution through the side-arm of a three-way stopcock connected to the infusion syringe. Doses of 0.4 to 1.0 mg were given, each injection taking 5 to 10 sec.

The effect of intra-arterial nicotine on the blood flow through the skin and the muscle of the forearm was determined in four subjects by following the changes in oxygen saturation of venous blood samples taken from deep and superficial forearm veins located in the cubital fossa and which drained the muscle and skin of the forearm respectively (Roddie, Shepherd & Whelan, 1956, 1957).

Intra-arterial infusions of phenoxybenzamine (Dibenyline; Smith Kline & French), 250 μg/min for 6 to 8 min, propranolol (Inderal; I.C.I.), 0.1 mg/min for 4 min, hyoscine hydrobromide (Farmer Hill) 0.1 mg/min for 2 or 4 min, or hexamethonium bromide (Vegolysen; May & Baker), 2.0 mg/min for 5 to 7 min, were given in some experiments. The doses of all drugs are expressed in terms of their salts. The amounts of phenoxybenzamine, propranolol and hyoscine that were given were shown to be sufficient to abolish the responses to infusions of noradrenaline (0.1 μg/min), adrenaline (0.1 μg/min) and acetylcholine (10 μg/min) respectively.

In three subjects an upper-arm nerve block using 1% lignocaine (Webling, 1960) was carried out after the response to intra-arterial nicotine had been recorded and the flow had returned to resting levels. Anaesthesia was complete within 30 min and muscle paralysis within 45 min. Recovery commenced 3 to 4 hr after the block. When the block was fully effective a second injection of nicotine was given. In two of these subjects phenoxybenzamine was then introduced intra-arterially and a further dose of nicotine was administered.

Nicotine was given intra-arterially into the left arm in one subject who had undergone a bilateral cervical sympathectomy 4.5 years previously (Parks, Skinner & Whelan, 1961). The absence of sweating on body heating and of any response of the forearm and hand vessels to intra-arterial ephedrine demonstrated that this arm was still completely sympathetically denervated at the time of the present study. Some recovery of sympathetic tone was evident on the right side and constriction of the hand vessels occurred with intra-arterial ephedrine.

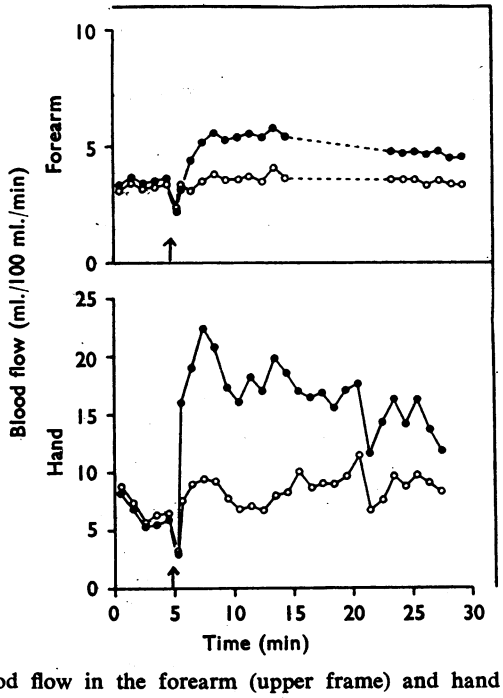

Fig. 1. Changes in blood flow in the forearm (upper frame) and hand (lower frame) caused by the administration of nicotine hydrogen tartrate (0.5 mg; at arrows) into the brachial artery of two normal subjects. ●, injected side; ○, control side.

Intra-arterial injection of nicotine was given into the completely denervated arm of a patient who had suffered brachial plexus avulsion nine months previously. The limb was devoid of sensory perception and motor function, and the vessels of the forearm did not show any constrictor response to ephedrine.

RESULTS

Twenty-two intra-arterial injections of nicotine (0.4 or 0.5 mg) were administered in nineteen normal subjects and forearm blood flow was measured. In every case there was an increase in blood flow in the injected forearm which was well established within 2 min of the injection of nicotine. The flow returned to the resting level in 15 to 45 min (Fig. 1, upper frame). In seven of the subjects the flow during the first minute after injection was unchanged. In three subjects there was a more rapid increase in flow which occurred in both the control and injected sides; it was transient in the control limb, and gave way to the longer lasting dilatation in the injected limb. In eight subjects an

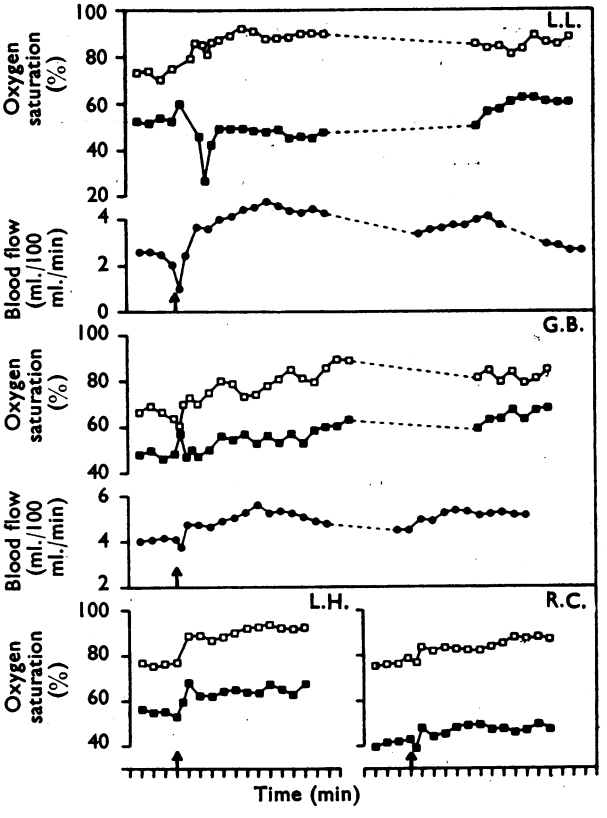

Fig. 2. The effect of intra-arterial injection of nicotine hydrogen tartrate (0.5 mg; at arrows) on the percentage oxygen saturation of blood samples taken from the veins draining the skin and muscle of the forearm in each of four subjects. The forearm blood flow changes in L.L. and G.B. are responses to a second injection of nicotine given approximately 1 hr after the first. □, percentage oxygen saturation of skin blood; ■, percentage oxygen saturation of muscle blood; and ●, forearm blood flow in ml./100 ml./min.

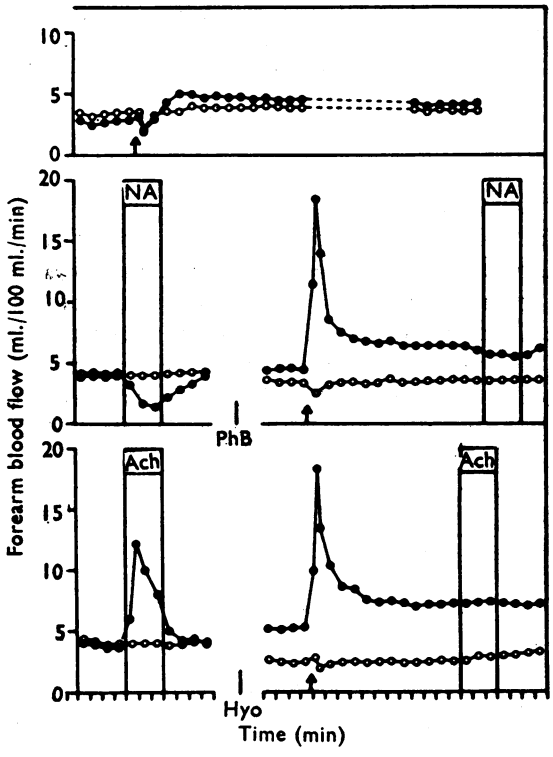

Fig. 3. The response of the forearm blood flow of B.E. to intra-arterial injection of nicotine hydrogen tartrate (0.5 mg; at arrows) before (uppermost frame) and after (middle frame) intra-arterial administration of phenoxybenzamine (PhB, 250 μg/min for 6 min). The response to intra-arterial noradrenaline (NA, 0.1 μg/min for 3 min) before and after phenoxybenzamine is also shown. Hyoscine hydrobromide (Hyo, 0.1 mg/min for 4 min) was then infused intra-arterially, while the phenoxybenzamine was still effective, and nicotine was again injected (lowest frame). Acetylcholine (Ach, 4 and 10 μg/min) was given before and after the hyoscine respectively. ●, injected side; ○, control side.

initial transient reduction in flow occurred, also in both forearms. In one subject an initial transient fall in flow was seen in the treated forearm only. All subjects complained of severe burning or tingling pain which spread over the entire forearm and which lasted approximately 30 sec after the injection of nicotine. The skin of the forearm was observed to be flushed shortly after the injection and this persisted for up to 45 min.

In nine experiments on eight subjects the blood flow through the hand was measured. Nicotine given intra-arterially caused an initial decrease in hand blood flow which occurred to an equal degree on both the treated and the control sides (Fig. 1, lower frame). This was followed by an increase in blood flow in the treated hand. Approximately 30 min elapsed before the flow returned to the pre-injection level. The injections of nicotine were accompanied by pain and tingling in the forearm, hand and fingers.

In four subjects venous blood samples were withdrawn from a superficial forearm vein (draining skin) and a deep vein (draining muscle) before and after the injection

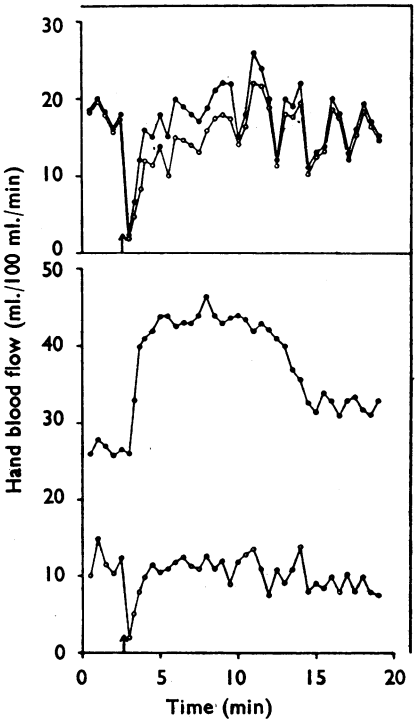

Fig. 4. The effect on the blood flow through the hand of R.H. of injection of nicotine hydrogen tartrate (0.5 mg; at arrows) into the brachial artery before (upper frame) and after (lower frame) intra-arterial phenoxybenzamine (250 μg/min for 6 min). ●, injected side; ○, control side.

of nicotine into the brachial artery of the same arm, and the percentage oxygen saturation of each sample was determined. The venous oxygen saturation was not measured simultaneously with blood flow since the collecting cuff pressure during flow measurements might divert skin venous blood into the muscle bed (Roddie *et al.*, 1956). The effect of nicotine on blood flow therefore was recorded in two of these subjects 1 hr later. Fig. 2 shows the results of these experiments. The oxygen saturation of the blood draining the skin of the forearm increased in every case, indicating vasodilatation. The changes in the oxygen saturation of muscle blood were variable. In three of the subjects there was an initial sharp increase in saturation and in one there was a slight decrease (R.C.). Subsequently the saturation gradually rose in three subjects, and in the fourth (L.L.) it fell below the resting level.

Phenoxybenzamine. Nicotine (0.5 mg) was administered intra-arterially before and after an intra-arterial infusion of phenoxybenzamine in six experiments on the forearm and four experiments on the hand. In the forearm nicotine given after phenoxybenzamine caused an initial large dilatation which was transient and gave way to the usual smaller but more sustained vasodilatation, and no constrictor response was seen (Fig. 3). In

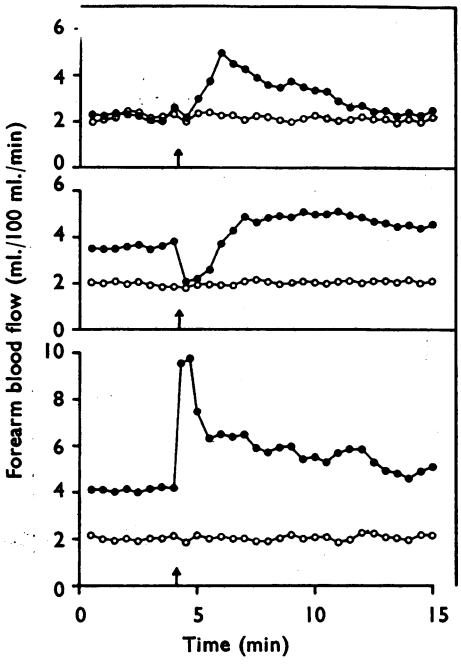

Fig. 5. The effect on forearm blood flow of C.J. of injection of nicotine hydrogen tartrate (0.5 mg ; at arrows) before (uppermost frame) and after (0.75 mg ; middle frame) block of the nerves to the arm with local anaesthetic solution. A third injection (0.75 mg) was given after administration of phenoxybenzamine (250 μg/min for 6 min) at a time when the nerve block was still effective (lowest frame). ●, injected side ; ○, control side.

the hand there was an immediate large vasodilatation (Fig. 4). The painful sensation caused by nicotine was somewhat reduced after phenoxybenzamine.

Nerve block. Forearm blood flow was measured in two of the subjects with upper arm nerve block and hand blood flow in the third. Before the nerve block was carried out nicotine (0.5 mg) produced a characteristic response in all three subjects—a transient slight fall in flow occurring in both treated and control forearm or hand during the first minute after injection followed by a vasodilatation on the injected side. Nerve block caused an increase of the blood flow in the forearm of 50% in one subject and 80% in the other and of 100% in the hand. Nicotine (0.75 mg in the forearm and 0.5 mg in the hand) now resulted in a constriction which was greater than before and persisted for about 2 min before the flow rose above the control level (Fig. 5). There was no pain associated with the injection of nicotine after the nerve block and no constriction was seen on the control side. In the two subjects in whom the forearm flow was measured, phenoxybenzamine was administered into the nerve-blocked arm and the nicotine injection again repeated. The constrictor response did not occur, being replaced by an immediate marked dilatation which began in the first minute. The flow subsided rapidly to a level about double the resting value and this more modest dilatation persisted for 15 to 30 min after the injection.

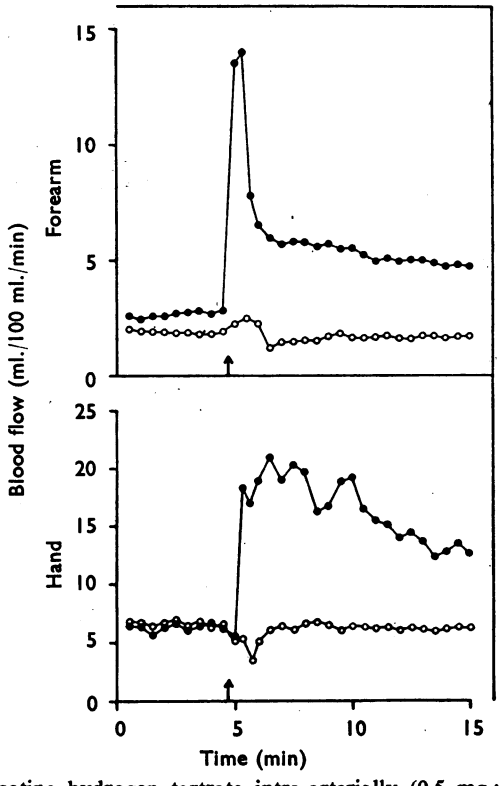

Fig. 6. The effect of nicotine hydrogen tartrate intra-arterially (0.5 mg; at arrows) on the blood flow through the forearm (upper frame) and hand (lower frame) of a sympathetically denervated limb (●). The opposite limb (○) had also been sympathectomized but showed evidence of recovery of innervation.

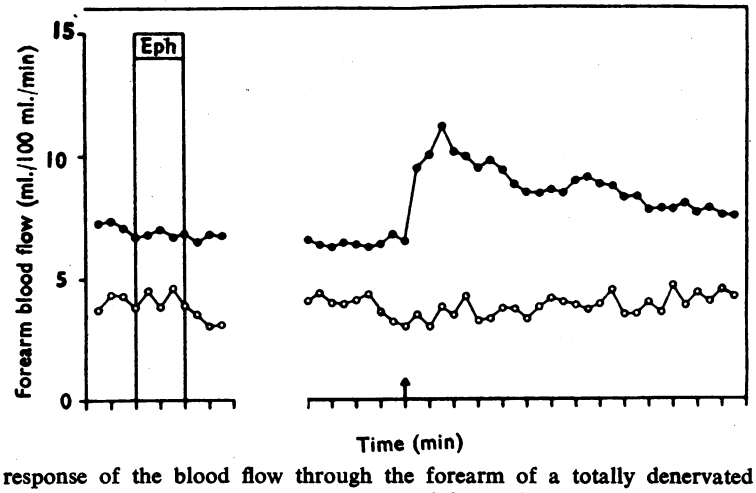

Fig. 7. The response of the blood flow through the forearm of a totally denervated limb of H.S. to nicotine hydrogen tartrate (1 mg; at arrow) injected into the brachial artery. Ephedrine hydrochloride (Eph, 500 μg/min) was also given intra-arterially into the denervated side. ●, denervated (injected) side; ○, normal (control) side.

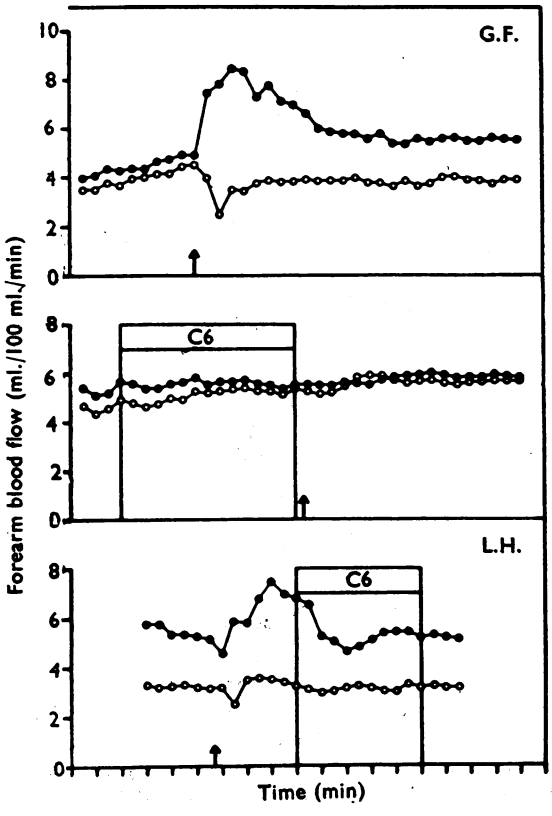

Fig. 8. The response of the blood flow through the forearm of G.F. to injection into the brachial artery of nicotine hydrogen tartrate (0.5 mg; at arrows) before (uppermost frame) and after (middle frame) intra-arterial infusion of hexamethonium bromide (C6, 2 mg/min). The lowest frame shows the effect, in a different subject (L.H.), of infusion of hexamethonium after the injection of nicotine. ●, injected side; ○, control side.

Sympathectomy. In the patient who had undergone sympathectomy four to five years previously the response of the forearm and hand vessels to nicotine (0.5 mg) injected into the brachial artery was identical to that seen in the normal subject after treatment with phenoxybenzamine. In the forearm an immediate large transient vasodilatation preceded a more modest and sustained increase in flow (Fig. 6, upper frame). In the hand there was an immediate and sustained dilatation. No constriction of the vessels occurred (Fig. 6, lower frame). The injection had the usual painful effect and a fall in the flow was seen in the opposite control hand, which had also been sympathectomized but in which there was evidence of recovery of sympathetic innervation.

Denervated limb. The response of the forearm vessels in the patient suffering from brachial plexus avulsion was similar to that seen in the sympathectomized subject. Nicotine (0.5 and 1.0 mg) injected into the brachial artery caused vasodilatation without any constrictor phase in either the injected or the control forearm, and the flow then gradually returned towards the resting level (Fig. 7).

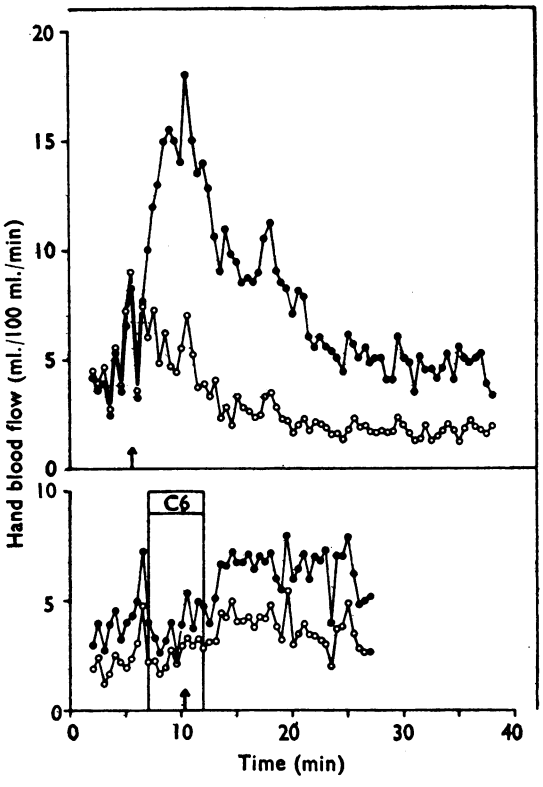

Fig. 9. The response of the blood flow through the hand of M.R. to injection of nicotine hydrogen tartrate (1 mg ; at arrows) into the brachial artery of a normal subject before (upper frame) and 3 min after the commencement of an infusion of hexamethonium (C6, 2 mg/min for 5 min, lower frame). ●, injected side ; ○, control side.

Hexamethonium. In two subjects nicotine was injected into the brachial artery before and after an intra-arterial infusion of hexamethonium, and forearm blood flow was recorded. In both, hexamethonium almost completely abolished the action of nicotine on blood flow and the pain was considerably less. The results in one of these subjects are illustrated in Fig. 8 (upper two frames). In a third subject the infusion of hexamethonium was begun during the vasodilatation produced by an intra-arterial injection of nicotine. The dilatation was terminated and the blood flow returned to the control level within 2 min of commencement of the infusion of hexamethonium (Fig. 8, lower frame).

Hexamethonium also abolished the effects of nicotine on the hand vessels. Fig. 9 illustrates the results on one of two subjects, who responded similarly. In the absence of hexamethonium a very large dilator response was produced by nicotine (1 mg), there being a slight bilateral constriction immediately on injection, accompanied by the sensation of severe pain and tingling. At 65 min after this first injection of nicotine, when the blood flow had almost, but not quite, returned to the control level, an intra-arterial infusion of hexamethonium was begun and maintained for 5 min. At 2 min

before the end of the infusion of hexamethonium, nicotine (1 mg) was injected. No pain was experienced and only a slight increase in flow occurred, which was probably due in part to a recovery from the effect of the hexamethonium, which produced a slight constrictor effect during its infusion.

Propranolol and hyoscine. Neither the sympathetic β-receptor blocking drug propranolol, nor the antiacetylcholine drug hyoscine, given intra-arterially, had any effect on the response of the forearm vessels to nicotine. One of the subjects who had received phenoxybenzamine was later given an intra-arterial infusion of propranolol (0.1 mg/min for 4 min). The response to the subsequent injection of nicotine was identical to that obtained after phenoxybenzamine alone. The same was true of two experiments in which hyoscine (0.1 mg/min for 2 and 4 min respectively) was given intra-arterially after the administration of phenoxybenzamine; one of these experiments is illustrated in Fig. 3.

DISCUSSION

The predominant effect of nicotine when injected into the vessels of the upper limb in these experiments was to cause a dilatation. The response was a complex one, however, and the presence of two minor constrictor components was apparent. The first of these was a sympathetic reflex response to the pain which was produced by nicotine injection. This occurred in both the control and the injected hands, but was absent in the control hand if the sensory nerves of the injected arm were blocked by local anaesthetic, when no pain was felt. The normal forearm vascular response to painful or stressful stimuli is a dilatation of the muscle vessels (Blair, Glover, Greenfield & Roddie, 1959; Barcroft, Brod, Hejl, Hirsjärvi & Kitchin, 1960) but there may also be a constriction of the vessels of the overlying skin. The presence of these two opposing effects probably accounts for the variations in the initial response of the total forearm blood flow after the injection of nicotine in the present experiments.

The second constrictor component was unmasked when the sensory nerves from the limb had been blocked. Injection of nicotine now caused a marked, though transient, vasoconstriction in both the hand and the forearm at a time when, because of the nerve block, no pain sensation was experienced, and flow through the control side was unchanged. This constrictor effect was clearly a local effect of nicotine. It appeared to be adrenergic in nature, since it was abolished by phenoxybenzamine, after which nicotine caused an abrupt and marked vasodilatation without any constrictor phase, and it was absent in the sympathetically denervated limb.

A constrictor action of nicotine on the smooth muscle of blood vessels attributed to release of noradrenaline has been described by a number of workers using a variety of preparations. Kottegoda (1953) showed that an antiadrenaline drug (tolazoline) abolished the constrictor effect of nicotine on the skin vessels of the rabbit ear. Hilton (1954) observed that the constrictor response to nicotine of the vessels in the cat's gastrocnemius muscle was abolished by phentolamine and after sympathetic nerve degeneration, and he attributed the constrictor action of nicotine to an axon reflex in adrenergic sympathetic fibres. Burn & Rand (1958) observed that the constrictor effect of nicotine on rabbit ear vessels was absent after treatment of the animal with reserpine.

Strömblad (1959) observed a constriction of hand vessels in man after intra-arterial infusions of nicotine which was abolished by dihydroergotamine and dibenamine. It has been suggested that chromaffin cells in the skin are the source of the noradrenaline liberated by nicotine (Strömblad, 1959 ; Burn, 1960). However, chromaffin cells do not appear to be present in the skin of the limbs in man (Matz & Skinner, 1962). It seems probable that in the present experiments nicotine caused constriction by stimulating peripheral sympathetic nerve endings, since no constriction occurred in forearm and hand vessels which were completely sympathetically denervated as a result of cervical sympathectomy or brachial plexus avulsion. This constrictor effect of nicotine therefore resembles that of ephedrine, methylamphetamine or tyramine on the peripheral vessels in man in that these too depend upon the integrity of the sympathetic nerves (Parks, Sandison, Skinner & Whelan, 1961 ; Scroop & Whelan, 1965).

There is a paucity of information on the dilator action of nicotine on blood vessels. Kottegoda (1953) described vasodilatation in the rabbit ear when nicotine was injected after treatment with tolazoline to block its constrictor effect. The cause of the dilatation was not discussed. Burn and Rand (1958) abolished the constrictor effect of nicotine on the rabbit ear vessels by treatment with reserpine and in a few instances a slight dilatation then occurred, but the significance and mechanism of the latter were not commented upon. Hilton (1954) reported dilatation of the vessels in the gastrocnemius muscle of the cat after small doses of nicotine given intra-arterially and attributed the response partly to an axon reflex in cholinergic vasodilator fibres and partly to a direct action of nicotine on the muscle vessels. A transient increase in skeletal muscle blood flow in the limbs in man after intravenous infusions of nicotine was described by Rottenstein *et al.* (1960) but the mechanism was not discussed. Long & Highgenboten (1964) noted dilatation of mesenteric vessels with arterial injection of nicotine, but the cause of the response was not elucidated. Strömblad (1959) illustrated a transient vasodilatation in the hand with intra-arterial infusions in man, but did not comment on the response. Jancsó, Jancsó-Gábor & Takáts (1961) demonstrated that the pain and hyperaemic effect of locally applied nicotine on the eye and nasal mucosa of animals was blocked after administration of hexamethonium and similar agents and concluded that this action of nicotine was purely neurogenic in nature and due to the excitation of sensory nerve endings. Coon & Rothman (1941) provided evidence that an axon reflex mechanism in the sympathetic nerve is responsible for the sudomotor response to intradermal injection of nicotine sulphate in man.

In the present series of experiments a dilator action of nicotine on the vessels of the hand and forearm was the predominant response. It was seen in every instance, and in the case of the forearm occurred both in the skin and the muscle.

The finding that the vasodilator action of nicotine was present after blocking conduction in the nerve trunks of the upper arm indicated that this was a local action of nicotine in the limb and not a central reflex effect. Its persistence after treatment of the limb with phenoxybenzamine and propranolol indicated that the response was not adrenergic in nature while its presence in the sympathetically denervated limb showed that it was not dependent on the peripheral sympathetic nerves. Since the dilator action was unimpaired in the completely denervated limb it cannot be attributed to a somatic nerve axon reflex. The dilatation was not cholinergically mediated since it was not affected

by administration of hyoscine in doses which effectively abolished the response of the limb vessels to large doses of acetylcholine. It must be concluded, therefore, that the dilator action of nicotine on the blood vessels of the hand and forearm in man is most probably a direct local effect on the smooth muscle.

Hexamethonium abolished both the constrictor and dilator effects of nicotine. There is no evidence that sympathetic ganglion cells are present in the limbs in man, and it is therefore unlikely that the abolition of the constrictor effect of nicotine is due to the ganglion-blocking action of hexamethonium. Hexamethonium blocked the action of nicotine in stimulating sensory nerve endings in the present study, and Keele & Armstrong (1964) showed that it abolished the pain caused by nicotine applied to the blister base. Ferry (1963) found that it abolished the excitation of sympathetic nerve endings by acetylcholine. It seems likely that the action of hexamethonium in abolishing the constrictor effect of nicotine is a peripheral one and occurs at the sympathetic nerve endings. The vasodilator action of nicotine does not appear to be due to stimulation of sensory nerve endings since it still occurred in the completely denervated limb. If it is accepted that the dilator action of nicotine is exerted directly on the vascular smooth muscle, then this action of nicotine too is antagonized by hexamethonium.

SUMMARY

1. Nicotine given intra-arterially into the brachial artery in man has three distinct effects on the blood vessels of the hand and forearm.

2. The predominant effect is a long lasting dilatation of the vesels of both skin and muscle. This is not influenced by hyoscine, phenoxybenzamine or propranolol and is present in sympathectomized and denervated limbs. It therefore appears to be due to a direct action of nicotine on the blood vessels.

3. A reflex sympathetic constriction of skin vessels and dilatation of muscle vessels is caused by the pain which accompanies the injection of nicotine. This reflex response to pain is bilateral, but is absent from the control side if nicotine is injected into a nerve-blocked or denervated limb.

4. An initial vasoconstriction is produced by stimulation of the peripheral sympathetic nerve fibres. This action is present in the acutely nerve-blocked limb but is blocked by phenoxybenzamine and is absent in sympathectomized and denervated limbs in which the sympathetic nerves have degenerated.

5. Both the constrictor and the dilator effects of nicotine are abolished by the prior administration of hexamethonium bromide, which also markedly reduced or abolished the pain.

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