EFFECT OF INTRA-ARTERIALLY ADMINISTERED NICOTINE ON THE BLOOD FLOW IN THE HAND

BY

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It is a well-known fact that smoking produces vasoconstriction in the human skin. Intravenous injections of nicotine in doses corresponding to those assumed to be absorbed after smoking a single cigarette cause a vasoconstriction comparable to that caused by smoking a cigarette (Maddock and Coller, 1933). The vasoconstriction following smoking has therefore been attributed to the nicotine content of the smoke. Smoking did not cause vasoconstriction in sympathectomized limbs or in limbs after blocking the sympathetic nerves (Maddock and Coller, 1933 ; Roth *et al.*, 1944). Consequently the action of nicotine was thought to be mediated via the sympathetic nerves. So far there has been no indication of a direct peripheral vascular action of nicotine in man. In animals, however, it has repeatedly been shown (for references see Burn and Rand, 1958) that nicotine can excite the smooth muscle of blood vessels when applied direct to the vessels in an organ bath or when given intra-arterially. This effect could be evoked consistently on frog and rabbit vessels but not regularly in the dog.

Methods

Thirteen experiments were made on 11 healthy subjects (seven males and four females).

Throughout the experiment the subject was lying on a couch in a silent room. The room temperature was kept relatively constant during each experiment, but varied between 21 and 24° C. in the different experiments. All drugs were injected through a "polythene" tube introduced into the left brachial artery at the elbow level as described by Bernéus *et al.* (1954). Saline solution or nicotine bitartrate dissolved in saline solution (*p*H about 7) was given in a single injection or with an infusion apparatus at a rate of 1.67 ml./min. Injections of nicotine, hexamethonium bromide, dihydroergotamine, pentolinium tartrate, or dibenamine hydrochloride were given in a volume of 1 ml. of saline solution. The blood flow in the left hand (catheter in left arm), and in a few experiments in the right hand as well, was measured with a venous occlusion plethysmograph. The blood flow was estimated intermittently. Each estimation consisted of five to eight readings taken during one to two minutes. The temperature of the water in the plethysmograph was 32° C.

Results

The intra-arterial injection (Fig. 1) or infusion of nicotine was found to cause vasoconstriction in the hand of the injected limb. The response ensued within a few seconds after the administration and could be repeated several times. The response could be graded by varying the dose given. After a single dose the vasoconstriction lasted only for a short time. No effect was discernible in the contralateral hand.

The infusion of nicotine at a rate of 16.7 μg./min. caused vasoconstriction in three subjects. With an infusion of 83.5 μg./min. vasoconstriction was noted in four further subjects, while the remaining four did not respond measurably to this dose, whereas a single injection of 100 μg. of nicotine was followed by a reduced blood flow. The injection of a corresponding volume of saline had no such effect. Two of the 11 subjects were heavy smokers (more than the equivalent of 30 cigarettes a day), two were medium smokers (5–15 cigarettes a day), and the rest were non-smokers or occasional smokers (a few cigarettes a month). No correlation was found between smoking habit and sensitivity to the vasoconstrictor effect of nicotine. Thus one of the heavy smokers responded to the infusion of 16.7 μg./min., while the other did not respond to the infusions but to the single injection of 100 μg. Infusions of more than 83.5 μg./min. were not regularly used, since such amounts (167 μg./min. was tried) were found to cause an unpleasant pricking sensation in the arm peripheral to the site of the catheter.

Several of the subjects remarked spontaneously on a chilling sensation in the injected limb. This sensation was experienced only during administration of doses of nicotine which caused vasoconstriction as measured plethysmographically.

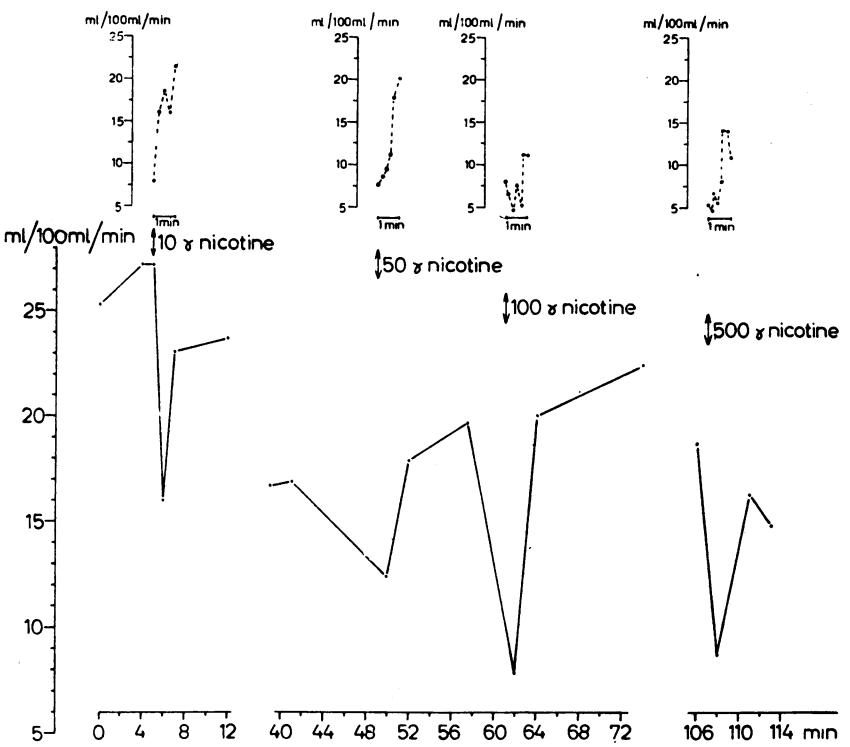

FIG. 1.—In the lower part of the figure is shown the effect of injections of nicotine bitartrate on blood flow in the hand. Nicotine was dissolved in 1 ml. of saline solution. Control injections of 1 ml. of saline solution were given. The upper part shows the readings during one minute following the injections of nicotine, starting 15 seconds after the injection.

Injection of hexamethonium intra-arterially abolished the effect of nicotine as shown in Fig. 2. Pentolinium tartrate (2 mg. intra-arterially) also blocked the vasoconstrictor effect of nicotine. Dihydroergotamine (0.5 mg. intra-arterially) and dibenamine (4 mg. intra-arterially) also prevented the vasoconstriction following infusion of nicotine. However, the injection of dihydroergotamine by itself caused a marked reduction in blood flow. This reduction was greater than that caused by the previous infusion of nicotine, and therefore no firm conclusion can be drawn regarding the blocking effect of this drug. The other three drugs given intra-arterially did not have any marked effect of their own on the blood flow.

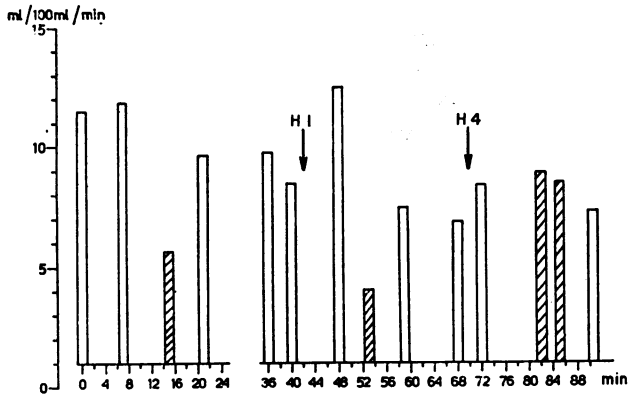

FIG. 2.—Blood flow in the hand during infusion of saline or nicotine bitartrate (83.5 μg./min.). Hatched columns denote nicotine. At the arrows 1 and 4 mg. of hexamethonium bromide were injected.

Discussion

Nicotine has been thought to cause a peripheral vasoconstriction by way of the sympathetic nervous system. The present report shows that nicotine causes an immediate vasoconstriction in the human hand when injected into the brachial artery. This effect is likely to be due to a direct peripheral action of nicotine, especially as vasoconstrictor responses were absent from the contralateral hand.

According to the calculations of Boyle *et al.* (1947), based on the findings of Baumberger (1923), smoking of cigarettes with inhalation will give an absorption of nicotine equivalent to 2 mg. of nicotine bitartrate a minute. The flow in the brachial artery at the site used for infusion may be about one-hundreth of the cardiac output, and hence smoking would correspond to an infusion of some 20 μg./min. in this artery. In the present experiments this was just about the threshold dose for vasoconstriction in certain individuals. Moreover, it is quite possible that during prolonged smoking there may be an accumulation of nicotine in the blood, causing a higher dosage than calculated above. It is therefore likely that in some individuals the amount of nicotine absorbed during smoking is big enough to elicit a direct peripheral effect. These assumptions and calculations are not necessarily contradictory to earlier reports that sympathetic blockade abolishes the vascular effect of smoking, since there are great individual variations in sensitivity, and the early experiments with sympathetic blocking were made in only a few cases.

The mechanism of the peripheral action of nicotine is not known. However, the present observation that sympathicolytic agents prevent the vascular effect of nicotine is compatible with the assumption that nicotine acts by release of sympathicomimetic substances (for references see Burn and Rand, 1958). These substances may be released from the system of chromaffin cells lying close to the small vessels of the human skin (Adams-Ray and Nordenstam, 1956) or they could be released from the store which has been found in the arterial walls (Schmiterlöw, 1948). A release from a chromaffin system would be consistent with the finding that ganglion-blocking agents prevent the effect of nicotine.

Another possible mechanism of the peripheral action of nicotine would be by excitation of a peripheral nervous plexus containing ganglion cells and adrenergic terminals. But so far no such peripheral nervous plexus has been definitely demonstrated (Folkow, 1956).

Summary

Nicotine was found to cause vasoconstriction in the hand when injected into the brachial artery. The threshold doses varied greatly between individuals, but, at least in some, the amount of nicotine assumed to be absorbed during smoking would be enough to cause vasoconstriction via a local mechanism. Sympathicolytics and ganglion-blocking agents abolished the effect of nicotine. This appears consistent with the assumption that nicotine causes a release of sympathicomimetics from the chromaffin system in the human skin, but could also be explained by the existence of a peripheral nervous plexus containing ganglion cells.

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In a sophisticated society the parents to whom a mentally subnormal child is born have a sad and difficult adjustment to make. Several books and pamphlets have appeared in recent years to help them " fashion from their disappointment a hope and a purpose " to give them new strength and understanding. These words are taken from the opening chapter of a handbook recently published for the Australian Council of Organizations for Subnormal Children (*The Subnormal Child at Home*, Macmillan, 5s.). The authors are F. J. Schonell, J. A. Richardson, and T. S. McConnel. They give a clear account, with neat illustrations, of how subnormal children can be helped to develop their faculties and, when possible, become self-supporting. The book would probably be of help to doctors who have to advise the parents of such children ; it would certainly be useful in the hands of intelligent parents confronted with this problem.