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EFFECTS OF NICOTINE AND TOBACCO SMOKE ON BLOOD PRESSURE AND RELEASE OF CATECHOL AMINES FROM THE ADRENAL GLANDS

BY

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Much has been written about the effects of tobacco smoke on the cardiovascular system of man and of experimental animals, but in none of these experiments has the amount of nicotine in the smoke been known. The present paper describes a method for introducing tobacco smoke from a cigarette, smoked under carefully controlled conditions, into the lungs of an artificially-ventilated cat. The pharmacological effects observed have been compared with those of nicotine acid tartrate injected intravenously.

METHODS

Experiments were made on forty-four cats of either sex weighing from 1.6 to 4.4 kg. In most of these experiments cats were anaesthetized with chloralose given intravenously in a dose of 80 mg/kg. In a few experiments pentobarbitone sodium was used as the anaesthetic (35 mg/kg, intraperitoneally) and in others the cat was made spinal during ether anaesthesia. Intravenous injections were made into the right femoral vein and blood pressure was recorded from the left femoral artery using a mercury manometer. In experiments on the denervated nictitating membrane, the right superior cervical ganglion was removed under aseptic conditions 10 to 18 days before the experiment. Contractions of the nictitating membrane were recorded by means of a lightly weighted frontal-writing lever giving a magnification of fifteen times. When the adrenal glands were excluded from the circulation, double ties were placed round the adrenal veins and the adrenal arteries, and the glands were usually removed completely. In a few experiments the right adrenal gland was so close to the vena cava that the veins and arteries were tied but the gland was left *in situ*. The carotid sinus nerve was located at its junction with the glossopharyngeal nerve and dissected down towards the carotid sinus. Ties were placed round the nerves so that they could subsequently be quickly found and cut. In experiments in which tobacco smoke was studied, the chest was opened in order to abolish spontaneous breathing.

The following drugs were used: (−)-adrenaline bitartrate, nicotine hydrogen tartrate and bretylium tosylate. All doses have been expressed as base.

Smoking pump. The method of introducing tobacco smoke into the lungs of a cat is illustrated in Fig. 1. Three small oscillating ventilation pumps were coupled together and the outlets of Pumps 2 and 3 were connected to a tube in the cat's trachea as shown. Pump 1 did not contribute to the ventilation of the animal and its purpose will be mentioned later. Pumps 1 and 2 were fitted with a three-way tap (the tap on Pump 1 cannot be seen in the Figure) so that air could be sucked either from the atmosphere or through a cigarette. A cigarette could be lit by holding a match against the tip on the " suck " stroke of the pump with the three-way tap closed to atmosphere. At the end of the " suck," the tap was then turned so that it was open to atmosphere. On the next " blow " stroke of the pump, this puff of smoke was delivered to the trachea if the cigarette was being smoked in Pump 2, or it was blown into the atmosphere if it was being smoked in Pump 1. A cigarette was smoked to a particular stage using Pump 1 and was then transferred to Pump 2, so that the next puff could be administered to the cat. In this way the rise in blood pressure caused

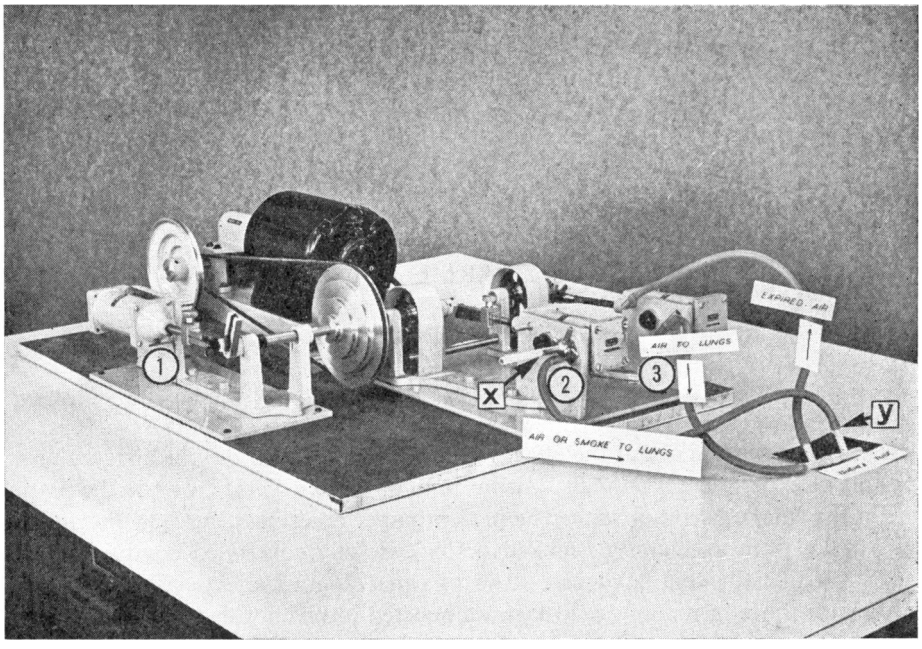

Fig. 1. Smoking and respiration pump used for introducing tobacco smoke into the lungs of a cat. See Methods for details.

by an individual puff of smoke could be matched accurately with the rise caused by a single intravenous dose of nicotine. The frequency of puff, usually 1/min, depended on suitable manipulation of the tap. The volume of puff could be varied by adjustment of the stroke volume of Pumps 1 and 2 and this was set at 25 ml. for most of the experiments. The duration of the puff depended on the speed at which the pumps were driven. The speed chosen was such that the duration of the suction stroke, assessed by connecting one of the pumps to a bubble manometer, was 2 sec. This rate of artificial ventilation was suitable for the cat. 40 to 50 ml. of air were usually used to inflate the lungs and the additional air to achieve this was supplied by Pump 3. If a U-tube immersed in an acetone : dry ice mixture was placed at x or y, smoke could be condensed and assayed for nicotine by the ultraviolet spectrophotometric method of Willits, Swain, Connelly & Brice (1960).

RESULTS

All experiments used a 2-sec duration of puff and a puff frequency of 1/min, as these parameters have been reported to approximate to the way in which the majority of British smokers smoke their cigarettes (Bentley & Burgan, 1961). Cigarettes used in these experiments were made from a blend of several different tobaccos currently used in the manufacture of British cigarettes (T1 cigarettes), except in the experiment of Fig. 4. The nicotine content of the smoke, when T1 cigarettes were smoked with different puff volumes, is shown in Table 1. A line was marked on the cigarettes 20 mm from one end, so that cigarettes could be smoked accurately to a butt length of 20 mm. The burning tip usually crossed this line on the 10th, 11th or 12th puff, which corresponded to smoking times of 9, 10 or 11 min. It was possible, however, for the burning tip to cross the 20-mm line just before taking a puff in which case n puffs would be recorded for a smoking time of n min.

TABLE 1

NICOTINE CONTENT OF THE MAINSTREAM SMOKE OF T1 CIGARETTES

The cigarettes were smoked in the apparatus illustrated in Fig. 1 to a butt length of 20 mm with a puff duration of 2 sec and a puff frequency of 1/min. * If smoke was condensed at y, instead of at x (see Fig. 1), the nicotine content of the smoke was only 70 to 80% of these amounts

Puff volume (ml.)	Average time to smoke (min)	Average nicotine: In the smoke per cigarette (mg)	Average nicotine: Per puff (mg)
35	9	2·5	0·25
30	10·4	2·3	0·20
25	10·2	1·96*	0·17*
20	11	1·64	0·14

The mid-puff of a cigarette was the puff which caused the burning tip to cross a line midway between the 20-mm butt line and the other end of the cigarette. Five cigarettes only were used for each determination and the figures quoted in columns 2, 3 and 4 are therefore liable to some error; for example, a 10% variation in smoking time was not uncommon. If the smoke was condensed at y, instead of at x (see Fig. 1), the nicotine content of the smoke was less by 20 to 30%. This loss presumably occurred in the pump when the smoke was in contact with the lubricated metallic cylinder. Increasing the puff volume from 20 to 35 ml. increased the total nicotine per cigarette by about 50%, the nicotine per puff by about 80%, and reduced the time required to smoke a cigarette to a fixed butt length by 20%.

The effect of tobacco smoke on the blood pressure of the spinal cat is shown in Fig. 2. Eleven puffs of a cigarette at 1-min intervals caused a rise in blood pressure similar to that

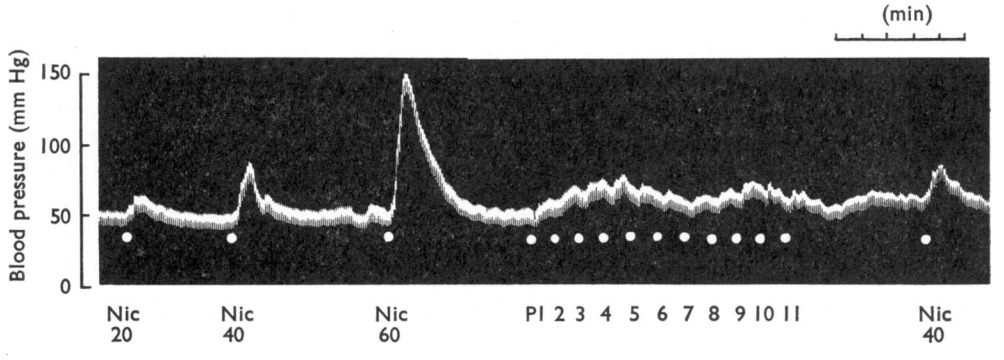

Fig. 2. Spinal cat, 2.6 kg. Record of blood pressure in femoral artery. Nic = nicotine, with doses as μg/kg of base injected into the femoral vein. P1 to P11 are puffs of tobacco smoke given at 1-min intervals.

produced by 30 μg/kg or 78 μg of nicotine base intravenously. The spinal cat was not sensitive enough for the assay of a single puff of smoke. After the smoking of a whole cigarette, 40 μg/kg of nicotine base intravenously had much the same effect as at the beginning of the experiment, showing that the tobacco smoke had not blocked the response to nicotine.

The cat anaesthetized with chloralose was generally very much more sensitive to nicotine. Thus, in Fig. 3 is shown the effect of smoking a whole cigarette in a similar way to the experiment illustrated in Fig. 2. Even though the blood pressure was unusually low for a cat anaesthetized with chloralose, each puff of tobacco smoke caused a striking rise of blood pressure. At the left-hand side of the kymograph tracing is shown the effect of the 6th puff of a cigarette smoked through a Whatman glass-fibre paper disc of pore size such that only the vapour phase of the tobacco smoke passed through it. For the 7th puff, 1 min later, the filter was removed. This experiment showed that the pharmacological pressor activity of tobacco smoke was in the particulate phase of the smoke.

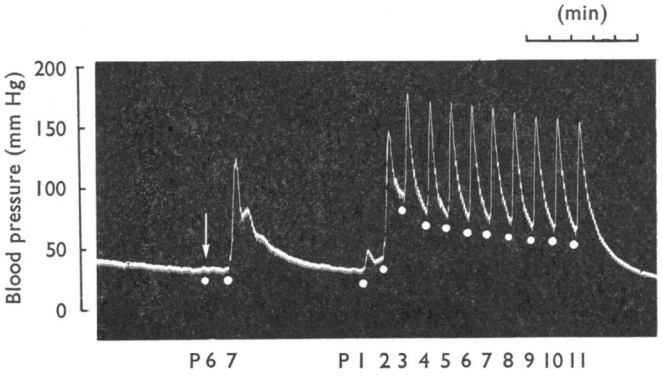

Fig. 3. Cat, 4.4 kg, chloralose anaesthesia. Record of blood pressure as in Fig. 2. P6 (arrow) was the sixth puff of a cigarette smoked through a Whatman glass-fibre paper disc. P7 was the next puff of the same cigarette with the filter removed. P1 to P11 show the effect of eleven puffs of tobacco smoke on the blood pressure of a cat under chloralose anaesthesia. Note that the response is completely different from that of the spinal cat (Fig. 2).

Fig. 4 shows the result of a similar experiment to that illustrated in Fig. 3 except that the cigarettes used were made from tobacco containing about one-thirtieth of the usual amount of nicotine. Each of the first seven puffs caused a progressively larger rise in blood pressure; the rise caused by puffs 8 and 9 was about the same as that caused by puff 7. The assay of individual puffs is illustrated in Fig. 5 which shows the increases of blood pressure produced by 22, 44, 66 and 88 μg of nicotine (5, 10, 15 and 20 μg/kg, respectively) injected intravenously. P2 shows the rise produced by the second puff of a cigarette which was approximately the same as that produced by 44 μg of nicotine (10 μg/kg). P12, the last puff of the same cigarette, caused a rise greater than that of 88 μg of nicotine (20 μg/kg), and approximately equal to the effect of 25 μg/kg of nicotine intravenously. P7, the mid-puff of another cigarette (not shown on Fig. 5), corresponded to a dose of about 88 μg of nicotine (20 μg/kg) intravenously. If the rise in blood pressure caused by tobacco smoke is due solely to its nicotine content this result indicates that the last puff of a cigarette smoked under the standard conditions of the experiment contains two- to three-times as much nicotine as the first puff.

The threshold intravenous dose of nicotine required to contract the denervated nictitating membrane of the spinal cat in an earlier series of experiments was 22 ± 5 μg/kg (mean and standard error), the lowest threshold being 8 μg/kg and the highest 42 μg/kg (Armitage & Milton, 1965). With the brain of the animal destroyed, any release of adrenaline was

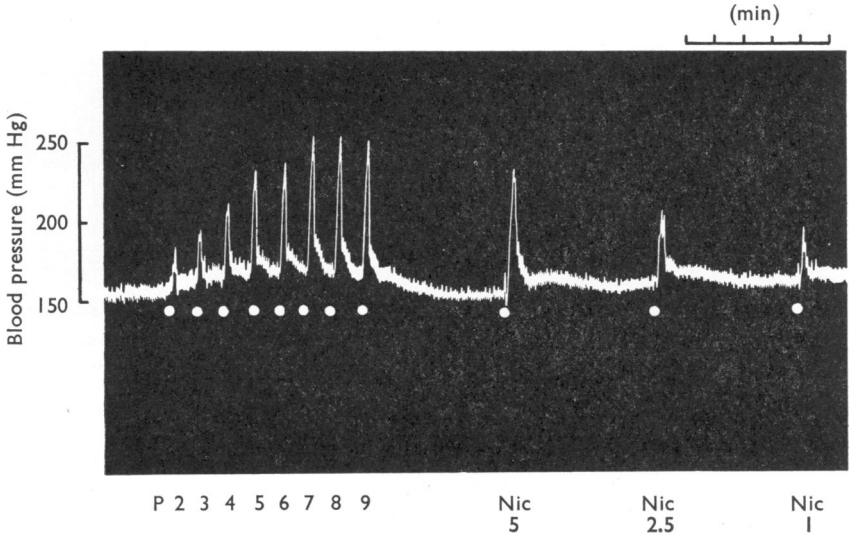

Fig. 4. Cat, 3.4 kg, chloralose anaesthesia. Record of blood pressure as in Fig. 2. P2 to 9 show the effect on blood pressure of the 2nd to the 9th puff of a cigarette made from tobacco of low nicotine content. Nic = nicotine, with doses as μg/kg injected into the femoral vein.

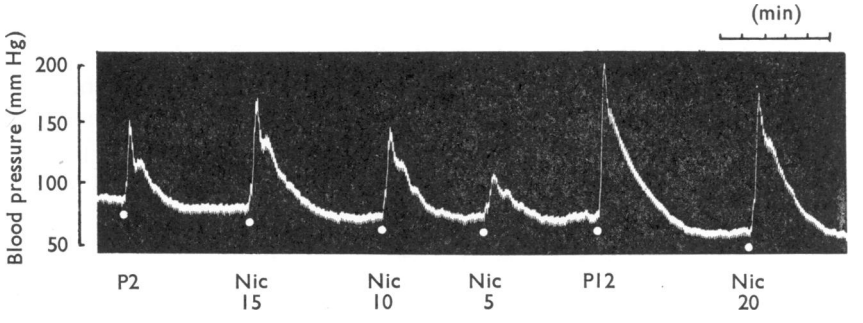

Fig. 5. Cat, 4.4 kg, chloralose anaesthesia, same experiment as for Fig. 3. Record of blood pressure as in Fig. 2. P2, P12 = assay of individual puffs (2nd and 12th) of tobacco smoke from the same cigarette. Nic = nicotine, with doses as μg/kg base injected into the femoral vein.

presumably due to a direct action of nicotine on the adrenal glands. It was therefore of interest to determine the threshold intravenous dose of nicotine in the cat anaesthetized with chloralose. It was found to be 8 ± 2 μg/kg, the lowest threshold being 2.5 μg/kg and the highest 17.5 μg/kg. The experiment, illustrated in Fig. 6, shows the effect on this threshold of cutting the spinal cord at the level of the second cervical vertebra. In the normal preparation (*a*) the threshold dose of nicotine to contract the nictitating membrane was about 2.5 μg/kg. After cutting the spinal cord (*b*), it was raised to slightly less than 10 μg/kg and, after removing the adrenal glands (*c*), it was raised still higher to between 20 and 40 μg/kg. The nictitating membrane was slightly more sensitive to adrenaline, however, in (*c*) than it was in (*b*). The contraction of the nictitating membrane by doses of nicotine less than 20 μg/kg was clearly due to a release of catechol amines from the adrenal

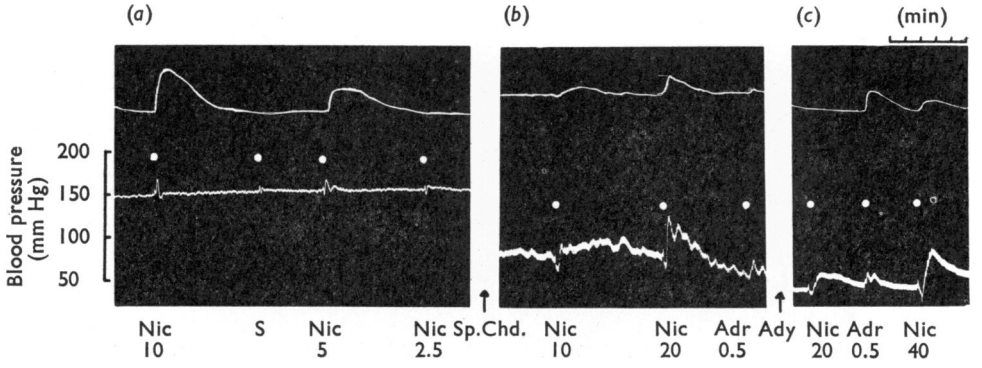

Fig. 6. Cat, 3.2 kg, chloralose anaesthesia, right superior cervical ganglion removed 18 days earlier. Top trace: contractions of denervated nictitating membrane. Bottom trace: femoral blood pressure. Nic = nicotine, S = saline, Adr = adrenaline; doses are expressed as μg/kg of base injected into the femoral vein. Between (*a*) and (*b*) the spinal cord was cut at the level of the 2nd cervical vertebra (Sp.Chd.). Between (*b*) and (*c*) both adrenal glands were removed (Ady). Time intervals: between (*a*) and (*b*), 30 min; (*b*) and (*c*), 45 min.

glands, since adrenalectomy abolished the response. In Fig. 7, however, exclusion of the adrenal glands was without effect on the pressor response of 5, 10 and 15 μg/kg of nicotine. The amount of catechol amines released by these low doses of nicotine was therefore insufficient to contribute to their pressor action. Bretylium, 2.5 mg/kg, reduced the pressor response but, unlike hexamethonium, did not abolish it. A dose of nicotine of the order of 5 μg/kg has no pressor action in a spinal cat. On this preparation, doses of nicotine which cause a moderate rise of blood pressure (50 μg/kg) are actually potentiated by bretylium (Fig. 8). On the spinal cat, therefore, the pressor action of nicotine in doses up to 50 μg/kg is due to release of catechol amines from the adrenal glands. Higher doses can increase blood pressure by stimulation of sympathetic ganglia.

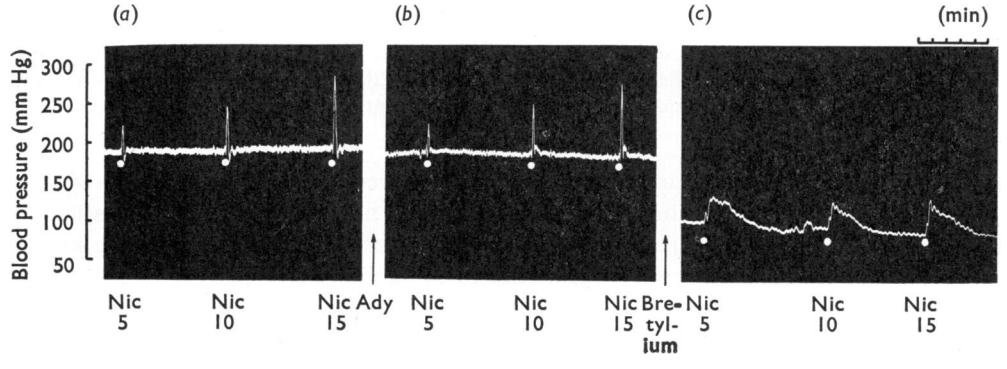

Fig. 7. Cat, 3.4 kg, chloralose anaesthesia. Record of blood pressure as in Fig. 2. Each section shows the pressor response of 5, 10 and 15 μg/kg of nicotine. Between (*a*) and (*b*) the adrenal glands were tied off and excluded from the circulation (Ady). Note that the responses in (*b*) were the same as those in (*a*). Between (*b*) and (*c*), bretylium (2.5 mg/kg) was administered intravenously and 35 min later (*c*) the pressor responses of nicotine were reduced. Time interval between (*a*) and (*b*), 45 min.

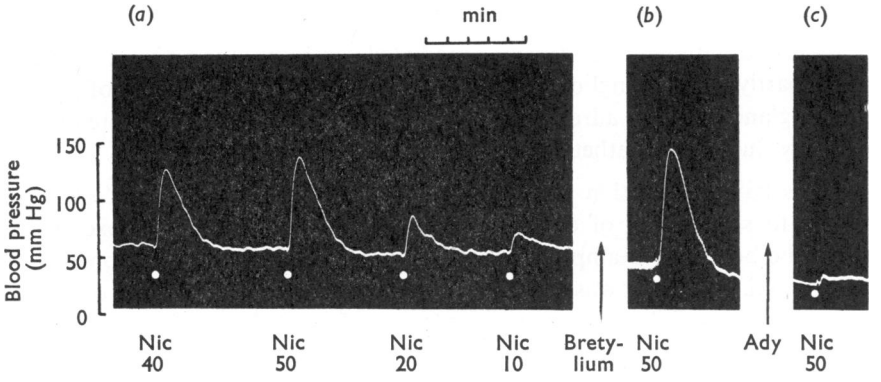

Fig. 8. Spinal cat, 3.2 kg. Record of blood pressure as in Fig. 2. Nic = nicotine, with doses as μg/kg of base injected into the femoral vein. Between (*a*) and (*b*) bretylium (2.5 mg/kg) was administered intravenously. Between (*b*) and (*c*) the adrenal glands were tied off and excluded from the circulation (Ady). 30 min after this dose of bretylium the pressor response to nicotine was potentiated (*b*). Time interval between (*b*) and (*c*), 40 min.

In two experiments, the smallest dose of nicotine capable of contracting the innervated nictitating membrane of the cat anaesthetized with chloralose was 40 μg/kg. When the superior cervical ganglion was removed acutely (Fig. 9, between *b* and *c*), the effect of 40 μg/kg of nicotine on the nictitating membrane was abolished and the effect of 80 μg/kg was reduced. The effect of 80 and 120 μg/kg was abolished by adrenalectomy (between

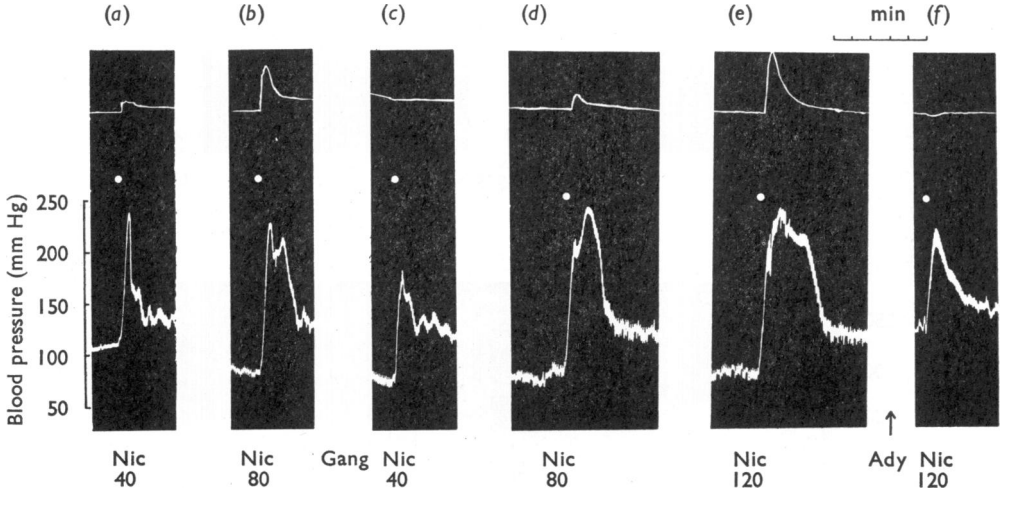

Fig. 9. Cat, 3.7 kg, chloralose anaesthesia. Top trace: contractions of the right normally innervated nictitating membrane. Bottom trace: femoral blood pressure. Nic = nicotine, with doses as μg/kg of base injected into the femoral vein. Between (*b*) and (*c*) the right superior cervical ganglion was removed (Gang). Between (*e*) and (*f*) both adrenal glands were removed (Ady). This experiment shows that the threshold dose of nicotine to cause a contraction of the nictitating membrane by direct stimulation of the superior cervical ganglion was not less than about 40 μg/kg. Time intervals: between (*a*) and (*b*), 32 min; (*b*) and (*c*), 15 min; (*c*) and (*d*), 30 min; (*d*) and (*e*), 12 min; (*e*) and (*f*), 20 min.

e and *f*). The contraction of the nictitating membrane caused by 40 μg/kg was therefore due to ganglionic stimulation, either direct or mediated centrally. The contraction caused by 80 μg/kg was partly due to ganglionic stimulation and partly due to release of adrenaline from the adrenal glands. After adrenalectomy, 120 μg/kg of nicotine still increased blood pressure, probably due to sympathetic ganglionic stimulation.

Several authors have stated that the pharmacological effects of the smallest doses of nicotine are due to stimulation of certain chemoreceptors that initiate reflexes affecting various parts of the body (for example, Fedorchuk, 1954; Gruhzit, 1957; Comroe, 1960; Anichkov & Belen'kii, 1963). It was therefore of interest to examine the effect of vagotomy and carotid sinus nerve section on the pressor response of small doses of nicotine. One of two similar experiments is shown in Fig. 10. The tracing shown in (*b*) was taken after cutting the vagi in the cervical region and after placing ligatures round the right and left carotid sinus nerves so that they could subsequently be found easily and cut. Vagotomy had no effect on the pressor responses of 5, 10 and 15 μg/kg of nicotine. After cutting the sinus nerves (*c*), the carotid occlusion response was abolished and the pressor response of these doses of nicotine was prolonged and reduced in size. Adrenalectomy (*d*) abolished the response of 10 μg/kg of nicotine, but 20 and 40 μg/kg of nicotine still caused some rise in blood pressure.

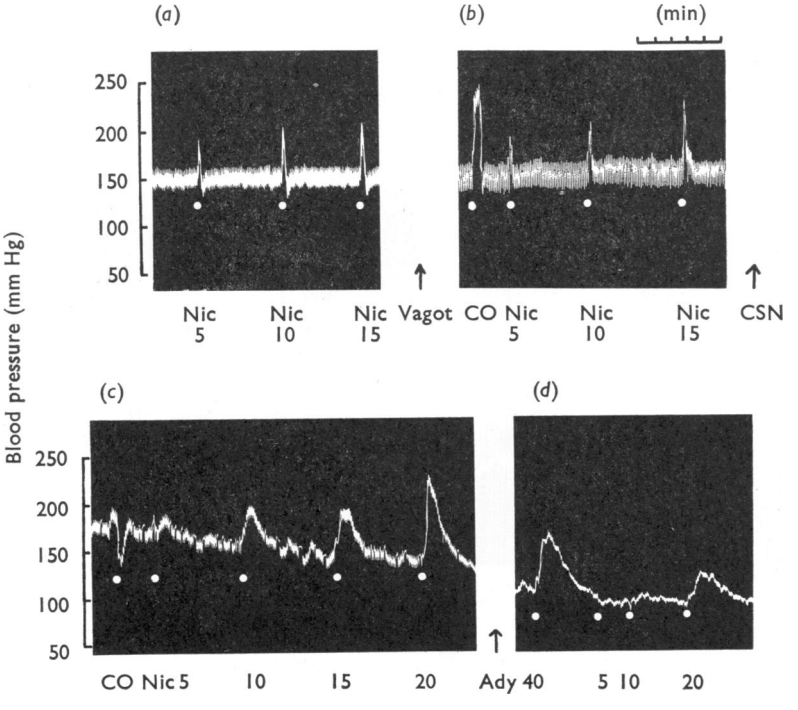

Fig. 10. Cat, 3.8 kg, chloralose anaesthesia. Record of blood pressure as in Fig. 2. Nicotine was injected into the femoral vein at the dots, with doses as μg/kg of base; S = saline; CO = occlusion of both carotid arteries for 30 sec. Between (*a*) and (*b*) both vagi were cut (Vagot), between (*b*) and (*c*) both carotid sinus nerves were cut (CSN) and between (*c*) and (*d*) both adrenal glands were removed (Ady). Time intervals: between (*a*) and (*b*), 21 min; (*b*) and (*c*), 15 min; (*c*) and (*d*), 32 min.

DISCUSSION

The importance of the present experiments is that the nicotine content of the smoke introduced into the lungs of a cat has been estimated with a fair degree of accuracy. The mid-puff of a cigarette should contain about the same amount of nicotine as the average of all the puffs, that is 0.17 mg (Table 1, column 4). The amount of nicotine in the mid-puff of a cigarette introduced into a cat, however, is only 70 to 80% of this quantity or 0.12 to 0.14 mg, on account of losses in the pump. In the experiment, part of which is illustrated in Fig. 4, the rise in blood pressure caused by the mid-puff of a cigarette was matched by an intravenous dose of 88 μg of nicotine. In six experiments, the lowest intravenous dose of nicotine that matched the mid-puff of a cigarette was 48 μg of nicotine (about one-third of the amount of nicotine in the mid-puff) and the highest was 110 μg (about four-fifths of the amount of nicotine in the mid-puff). As a rough approximation, therefore, the dose of nicotine in a puff of tobacco smoke may be expected to exert a similar pharmacological effect to half this amount administered intravenously. It should be noted that the rise in blood pressure following the administration of a puff of tobacco smoke was extremely rapid in onset and indistinguishable from the response to an intravenous injection of nicotine. The nicotine intake during the smoking of a cigarette is therefore likely to be equivalent to a series of small intravenous injections. The tobacco smoke exhaled by the cat was not assayed for nicotine and so it is not possible to state what proportion of nicotine in the tobacco smoke was actually absorbed. It should be stressed that the tobacco smoke was introduced into the trachea. Absorption could therefore only take place from the lungs and upper respiratory tract and not from the mouth.

The rise of blood pressure caused by tobacco smoke is undoubtedly due to a substance or substances with nicotine-like properties though whether the pressor action is due solely to its nicotine content cannot be stated with certainty. To do this it would be necessary to administer a known amount of nicotine as an aerosol of the same particle size as tobacco smoke, and compare the effects with smoke containing the same amount of nicotine. The nicotine in smoke is present as salt and base and this is an added complication. Even the smoke from cigarettes made from tobacco of low nicotine content caused a large rise in blood pressure (Fig. 4). In this particular experiment, the cat was unusually sensitive to nicotine and the threshold dose to cause a rise in blood pressure was less than 1 μg/kg. It is unfortunately not possible to remove nicotine from a given tobacco or tobacco smoke without removing many other constituents at the same time.

A puff of tobacco smoke drawn into the mouth of a human smoker probably contains not less than 0.1 mg and not more than 0.3 mg of nicotine. The results presented in this paper suggest that this is likely to be equivalent to an intravenous dose of about 50 to 150 μg, or 1 to 2 μg/kg body weight, and such a dose is taken at each puff. An intravenous dose of 1.5 μg/kg of nicotine given ten times at 1-min intervals to a cat had much less effect on blood pressure than a single dose of 15 μg/kg. Since the pharmacological analysis of the effects produced by a multiple dose of nicotine is not easy, it was decided to study the effects produced by single intravenous doses. Different species may, of course, differ in their sensitivity to nicotine. A single dose of 5 to 10 μg/kg of nicotine in a cat, however, would seem to be a realistic " smoking " dose and it is the pharmacological effects of doses of nicotine of this order of magnitude that are likely to be relevant to the pharmacology of tobacco smoking. A 25-ml. puff of tobacco smoke for a cat is obviously much larger than

a human smoking dose but at the present time it is not possible to administer less than this amount. For this reason, attention has been focused on the effects of small intravenous doses of nicotine rather than the effects of tobacco smoke itself.

Experiments on the denervated nictitating membrane of the cat anaesthetized with chloralose showed that the threshold intravenous dose of nicotine to cause a release of catechol amines from the adrenal glands was 8 ± 2 μg/kg (mean and standard error), the lowest threshold being 2.5 μg/kg and the highest 17.5 μg/kg. These thresholds were for a single rapid intravenous injection of nicotine. If a smaller dose was given five or ten times at 30-sec intervals, the denervated nictitating membrane contracted by about the same amount as after the larger single dose. Armitage & Milton (1965) showed that a slow continuous intravenous infusion of nicotine during 10 min had a similar effect on the denervated nictitating membrane as one-tenth to one-twentieth of the total amount of nicotine infused given as a single dose. These results indicate that the blood nicotine concentration can be raised most efficiently to a level at which the nicotine will exert a pharmacological effect by periodic injections of small amounts.

The present experiments indicate that the nicotine content of the last puff of a cigarette contains two to three times as much nicotine as the first puff. Thus if a smoker takes ten identical puffs of a cigarette, each successive puff will contain more nicotine than the preceding puff. A smoker has control, however, literally at his finger tips, of the amount of nicotine he can take into his mouth and it may be that he modifies his puff during the course of smoking a cigarette. According to data quoted by Larson (1960), absorption of nicotine by smokers who do not inhale is only about 15% of the nicotine entering the smoker's mouth. From the results presented here, it seems likely that only smokers who inhale deeply and rather frequently will attain a sufficiently high blood nicotine level to cause a release of catechol amines from the adrenal glands. Whether the amounts released have any physiological significance still remains to be elucidated.

In the spinal cat, a 25-ml. puff of tobacco smoke or an intravenous dose of 5 μg/kg of nicotine had only a small, or no effect, on blood pressure. In the chloralose cat, however, a striking response was frequently observed and this could always be abolished by hexamethonium or by cutting the spinal cord. An intact central nervous system was clearly necessary for the response. Of thirty-two cats under chloralose anaesthesia, fourteen were extremely sensitive to small intravenous doses of nicotine, typical responses being shown in Figs. 4, 7 and 10. Complete dose/response curves were not drawn but it was apparent that they were very steep. In the other eighteen experiments, the dose/response curves were much shallower and much larger doses of nicotine were required to produce a similar rise in blood pressure. Such an experiment is shown in Fig. 6, in which a 10-μg/kg dose of nicotine had very little effect on blood pressure. In these experiments, the cats were more sensitive to nicotine than a spinal animal and of similar sensitivity to a cat under pentobarbitone anaesthesia. Difference in sensitivity to nicotine in animals anaesthetized with chloralose and pentobarbitone is not surprising and has been reported by Westfall (1965), but the reason why low doses of nicotine in about half the cats caused only very small rises in blood pressure is not known. All the cats received an 80-mg/kg intravenous dose of chloralose and it is possible that some were more deeply anaesthetized than others, which could account for reduced sensitivity. The peak concentration of nicotine in the blood at

a target organ is also likely to be an important factor and this may vary greatly from animal to animal.

The various ways in which nicotine is able to cause a rise in blood pressure are well known. These include direct and indirect stimulation of the vasomotor centre; stimulation of sympathetic ganglia; release of catechol amines from the adrenal medulla or release of noradrenaline from local stores. Reflex stimulation of the vasomotor centre via the carotid body is generally thought to be the most important mechanism in the pressor response of the smallest doses of nicotine, though sympathetic stimulation and adrenal medullary stimulation are also thought to be contributory factors (Larson, Haag & Silvette, 1961). This statement, however, does not agree with the observations reported here. For example, the experiment illustrated in Fig. 7 clearly shows that the pressor responses of 5, 10 and 15 μg/kg of nicotine were entirely independent of the adrenal glands. The dose of nicotine required to contract the innervated nictitating membrane by stimulation of the superior cervical ganglion was not less than 40 μg/kg (Fig. 9). If the threshold dose for other sympathetic ganglia is similar, it is unlikely that a dose as low as 5 μg/kg could cause a rise in blood pressure by stimulation of sympathetic ganglia. In the experiments illustrated in Figs. 7 and 9, the vagus nerves and the carotid sinus nerves were intact. In Fig. 10, cutting both sinus nerves (which abolished the carotid occlusion reflex) did not abolish the pressor response to 5 μg/kg of nicotine, although there was a noticeable change in the onset and duration of response. Vagotomy did not affect the pressor response but, after cutting both sinus and vagus nerves, removal of the adrenal glands did abolish the rise in blood pressure. Under these experimental conditions the adrenal glands were therefore essential for the pressor response. These observations are not in complete agreement with those of Fedorchuk (1954), who found that, after exclusion of the carotid plexus by extirpation or by anaesthesia with 1% novocaine, the rise of blood pressure in the decerebrate cat caused by 6 μg/kg of nicotine was abolished. The rise caused by doses of 20 to 30 μg/kg was reduced, and the duration of the response was changed. Nor do they agree with the results of Gruhzit (1957), who found that section of both vagi and carotid sinus nerves usually abolished the hypertension caused by the minimally effective dose of nicotine injected directly into the right or left atrium.

The action of nicotine is obviously a complex one and probably involves more than a simple reflex action on the adrenal glands and blood vessels from the chemoreceptors of the carotid plexus as suggested by Fedorchuk (1954). The possibility therefore remains that a direct and an indirect stimulation of the vasomotor centre are involved in the pressor response of small intravenous doses of nicotine in the cat anaesthetized with chloralose. Solti, Márton, Hermann, Papp & Rév (1960), using a cross-circulation technique, also concluded that the electrocardiographic and circulatory changes caused by nicotine had a component of central origin. Heymans, Bouckaert, von Euler & Dautrebande (1932), on the other hand, found that a dose of nicotine as large as 1 mg was necessary to produce a vasomotor action of central origin in dogs.

SUMMARY

1. A method has been devised for introducing tobacco smoke containing a known amount of nicotine into the lungs of an anaesthetized cat.

2. The effect on blood pressure of a single puff of tobacco smoke is almost identical with the effect of half the amount of nicotine in the puff injected intravenously. The last puff of a cigarette contains two to three times as much nicotine as the first puff.

3. The results of these experiments on cats suggest that the amount of nicotine entering the blood of a smoker who inhales is likely to be in the range of 50 to 150 μg of nicotine per puff, which approximates to a dose of 1 to 2 μg of nicotine per kg body weight. Allowing for species variation, it is considered that an intravenous dose of 5 to 10 μg/kg in a cat is a fair approximation to a human smoking dose of nicotine.

4. It is probable, but impossible to be certain, that the intake of nicotine during the smoking of a cigarette is sufficient to cause a release of catechol amines from the adrenal glands in some smokers, particularly those who inhale deeply and frequently.

5. Small intravenous doses of nicotine caused in about half the observations a sharp rise in blood pressure of short duration. This response is never seen in the spinal cat in which the brain is destroyed and it does not appear to be entirely accounted for by stimulation of sympathetic ganglia, release of catechol amines from the adrenal glands or by chemoreceptor stimulation. The possibility remains that direct stimulation of the vasomotor centre is involved.

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