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A PRESSOR RESPONSE OF THE RABBIT TO NICOTINIC ACID

BY

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It has been reported that in man nicotinic acid administration in certain doses results in peripheral vasodilatation especially in the skin and upper trunk (Bean & Spies, 1940; Sollmann, 1957). Also intravenous injection of nicotinic acid in the dog results in a fall in arterial blood pressure (Hauschild, 1960).

During a study on the mechanism of vasodilatation caused by nicotinic acid injection, it was found that its effect on the arterial blood pressure of the rabbit had a pressor component. This was not observed in cats or dogs which showed only a fall in blood pressure. The present work was undertaken mainly to study the mechanism of the pressor response to nicotinic acid in the rabbit; a few experiments on its effect in the cat and dog are also reported.

METHODS

Rabbits of either sex weighing between 1.75 and 2.5 kg were anaesthetized with urethane (25% solution in 0.9% saline, 1 g/kg, intravenously into the marginal ear vein). Cats of either sex weighing between 2 and 6 kg were initially anaesthetized with ether; anaesthesia was then maintained with choralose (80 mg/kg, intravenously). Dogs of either sex weighing between 6 and 15 kg were initially anaesthetized with ether and anaesthesia was maintained with sodium barbitone (250 mg/kg, intravenously). Blood pressure was measured from a common carotid artery by a mercury manometer. Drugs were injected into a jugular vein in rabbits and into a femoral vein in cats and dogs, and washed in with a double volume of 0.9% saline. Heparin (1,000 u./kg) was injected intravenously. Throughout experiments, artificial ventilation was maintained with a pump.

Carotid sinus denervation and bilateral vagotomy. This was done in the rabbit by dissecting along the common carotid artery on each side until the origin of the internal and external carotid arteries just below the jaw was reached. The arterial fork was cleared completely of all adherent tissue by blunt dissection with forceps, thus ensuring that the carotid body with its nerve connexion had been removed. Bilateral vagotomy was done by cutting both vagi in the neck.

Drugs

Preparation of nicotinic acid and nicotinamide solution. Solutions of sodium nicotinate were prepared by dissolving nicotinic acid powder in warm sodium hydroxide solution to give a *p*H of 6.5 to 7.5 and a concentration of 200 to 400 mg/ml.; the solution was freshly prepared and kept at about 35° C before injection. Doses are expressed in terms of the acid, and the drug will be referred to as nicotinic acid. Nicotinamide solution was prepared by dissolving the powder in 0.9% saline to give 250 mg/ml. solution.

Reserpine solution. Reserpine solution was prepared by dissolving reserpine powder in the least necessary amount of glacial acetic acid and then distilled water was added to give a concentration of 5 mg/ml.

Other drugs. The following drugs were used (doses of salts are expressed as bases): acetylcholine chloride (Roche), adrenaline bitartrate (B.D.H.), atropine sulphate (B.D.H.), bretylium tosylate (Wellcome Research Laboratories), cocaine hydrochloride (B.D.H.), ergotamine tartrate (Roche), heparin (Evans), hexamethonium chloride (Fluka), histamine acid phosphate (B.D.H.), mepyramine maleate (Neoantergan, Specia), nicotinic acid (Fluka), nicotinamide (B.D.H.), noradrenaline bitartrate (Bayer), reserpine (Ciba), phenoxybenzamine (Dibenzyline, Smith Kline & French) and tolazoline (Priscol, Ciba). All drugs were injected intravenously.

RESULTS

Rabbits

Thirty rabbits were used. When nicotinic acid or nicotinamide were repeatedly administered, the interval between subsequent doses was 15 to 30 min. Nicotinic acid in a dose less than 20 mg/kg caused either no change or a slight rise in blood pressure. Injection of 30 to 300 mg/kg nicotinic acid had a marked action on blood pressure. The response varied with the dose and animal used. In ten rabbits nicotinic acid caused only a pressor response which started 12 to 20 sec after injection and lasted for 2 to 8 min. However, in twenty other rabbits nicotinic acid caused either a biphasic or a triphasic response. In these animals the primary phase of the response was a transient rise in blood pressure starting within 5 sec after injection and lasting for 3 to 15 sec followed by a return to control level or by a fall in blood pressure which lasted for 0.5 to 1.5 min. The secondary phase was a relatively sustained rise in blood pressure which started after 15 to 90 sec and lasted for 3 to 12 min depending on the dose. In some experiments, the initial response to nicotinic acid was a fall in blood pressure without a previous transient rise. The pressor component in the action of nicotinic acid was always observed whether it was preceded by a transient rise or by a fall in blood pressure and it was accompanied by tachycardia.

Nicotinamide in doses below 30 mg/kg did not cause any appreciable effect on blood pressure. Doses of 30 to 300 mg/kg caused a fall in blood pressure without any pressor component, proportional, both in intensity and duration, to the dose. In ten rabbits with small doses (50 to 100 mg/kg) the duration was 1 to 3 min. However, with larger doses (200 to 300 mg/kg) blood pressure began to return within 2 to 4 min to 20 to 30 mm Hg below the control level, but then took 8 to 15 min to return to this level (in

five rabbits) and in some experiments did not return quite to normal even after 30 min (in two rabbits).

Effect of mepyramine. It is known that histamine injection into the rabbit causes a pressor response (Sollmann, 1957) and it was thought that the pressor action of nicotinic acid in the rabbit might be due to release of histamine. Several experiments were performed to examine the effect of the antihistaminic drug mepyramine on the effect of nicotinic acid and nicotinamide. Fig. 1 shows that nicotinic acid (100 mg/kg) resulted in a monophasic pressor response and histamine (25 μg/kg) caused a rise in blood

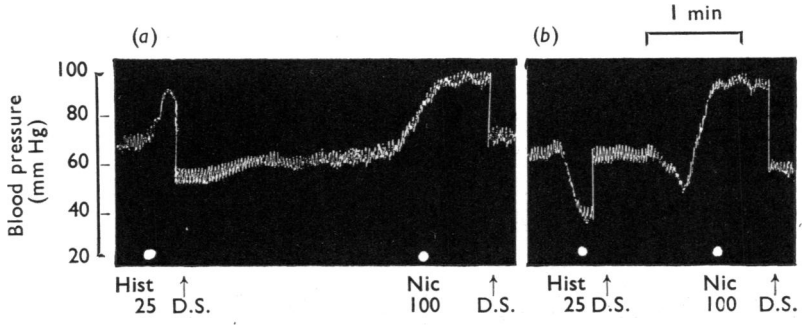

Fig. 1. Blood pressure of a rabbit (1.875 kg) anaesthetized with urethane. Doses in μg/kg, except for nicotinic acid in mg/kg. Between (a) and (b) mepyramine (2.5 mg/kg, intravenously). Time interval between (a) and (b) is 15 min. Histamine (Hist), nicotinic acid (Nic). D.S., drum was stopped. Note that mepyramine did not affect the action of nicotinic acid but it caused reversal of the action of histamine.

pressure followed by a fall. Mepyramine (2.5 mg/kg) was then injected; 15 min later histamine was injected and unexpectedly it resulted in a fall in blood pressure, i.e., there was histamine reversal, but the pressor response to nicotinic acid was unchanged, although preceded by a fall in blood pressure. In another experiment, nicotinic acid (200 mg/kg) caused a fall followed by a rise in blood pressure and histamine (25 μg/kg) caused a rise in blood pressure which was not followed by a fall. After mepyramine (2 mg/kg), histamine (25 and 50 μg/kg) caused a fall in blood pressure, but the biphasic response to nicotinic acid was not affected. In a third experiment, injection of histamine (10 μg/kg) caused a rise in blood pressure and nicotinic acid (100 mg/kg) caused a transient rise followed by a transient fall and then a sustained rise in blood pressure. Mepyramine (5 mg/kg) blocked completely the action of histamine (20 μg/kg) but did not affect the action of nicotinic acid. A second injection of mepyramine (2 mg/kg) did not affect the action of nicotinic acid while a third injection of histamine (40 μg/kg) caused a slight fall in blood pressure. This action of histamine (40 μg/kg) was blocked by a third injection of mepyramine (5 mg/kg), but again the action of nicotinic acid was not affected. Thus mepyramine did not affect the action of nicotinic acid. Similarly, the action of nicotinamide was not affected by mepyramine.

Effect of carotid sinus denervation and bilateral vagotomy. In order to examine the possibility that the pressor response to nicotinic acid might be due to a reflex action through the carotid sinus baroreceptors or carotid body chemoreceptors, nicotinic acid was injected into two rabbits before and after bilateral vagotomy and carotid sinus and body denervation. Fig. 2 shows that vagotomy alone had no significant effect on nicotinic acid action, but when both carotid sinuses were denervated the pressor action of nicotinic acid was slightly potentiated as was also the pressor response to adrenaline and the size and duration of the fall in blood pressure caused by nicotinamide.

Effect of atropine, vagotomy and hexamethonium. In four rabbits, atropine (1.25 to 4 mg/kg) did not affect the action of nicotinic acid, but diminished slightly the intensity and duration of the response to nicotinamide. Bilateral vagotomy in three rabbits slightly potentiated the pressor response of nicotinic acid. Hexamethonium (20 mg/kg) alone (in two rabbits) or after bilateral vagotomy (in two rabbits) prolonged the duration of the pressor response of nicotinic acid. In two rabbits, vagotomy and hexamethonium did not block the action of nicotinamide.

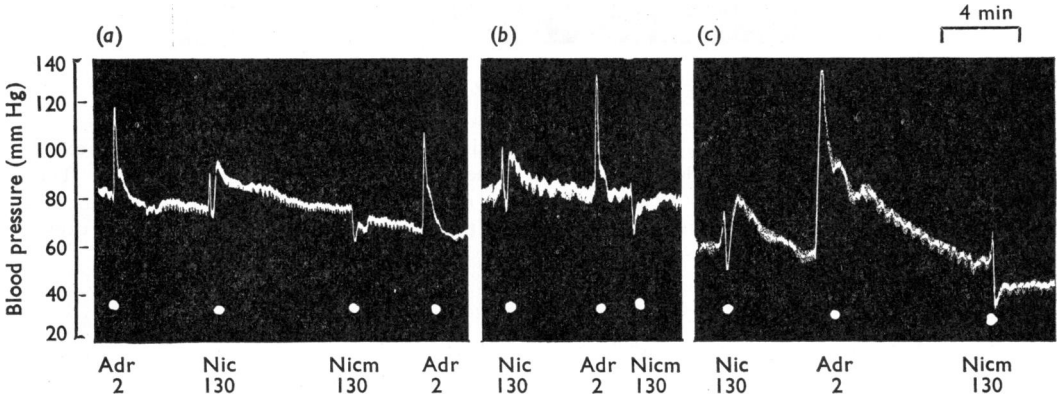

Fig. 2. Blood pressure of a rabbit (2.25 kg) anaesthetized with urethane. Adrenaline (Adr), nicotinic acid (Nic), nicotinamide (Nicm). (a) Before vagotomy. (b) After bilateral vagotomy. Note that vagotomy did not affect the action of nicotinic acid or nicotinamide. (c) After bilateral vagotomy and complete carotid sinus and body denervation. The action of nicotinic acid was exaggerated. Time interval between (a) and (b) is 10 min and between (b) and (c) is 20 min. Doses in μg/kg, except for nicotinic acid and nicotinamide in mg/kg.

Inhibition of nicotinic acid action by sympathetic α-receptor blocking agents

The possibility that the pressor response to nicotinic acid might be mediated by the liberation of catechol amines from body stores was supported by the observation that adrenaline antagonists blocked the action of nicotinic acid. Fig. 3 shows that phenoxybenzamine almost completely blocked the action of nicotinic acid. In ten experiments phenoxybenzamine (4 to 8 mg/kg) blocked almost completely the action of nicotinic acid as well as that of nicotinamide. Also ergotamine tartrate (0.75 mg/kg) and tolazoline (8 mg/kg) greatly diminished the action of nicotinic acid.

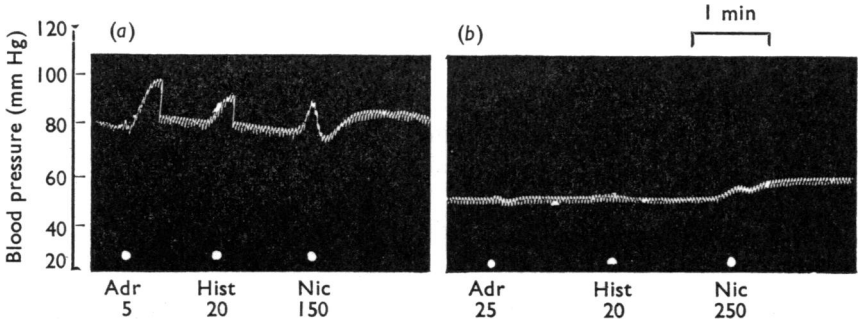

Fig. 3. Blood pressure of a rabbit (2 kg) anaesthetized with urethane. Adrenaline (Adr), histamine (Hist), nicotinic acid (Nic). Between (a) and (b) phenoxybenzamine (10 mg/kg, intravenously). Time interval between (a) and (b) is 30 min. Phenoxybenzamine almost completely blocked the action of nicotinic acid. Doses in μg/kg except for nicotinic acid in mg/kg.

Effect of cocaine

The effect of cocaine on the action of nicotinic acid was studied in two rabbits. In the first experiment, nicotinic acid (150 mg/kg) caused a relatively sustained fall followed by a secondary rise in blood pressure. Thirty min after cocaine injection (2.5 mg/kg) the secondary rise due to nicotinic acid and the pressor response due to adrenaline and noradrenaline were potentiated both in intensity and duration (Fig. 4). In the second experiment nicotinic acid (100 mg/kg) caused a rise with two pressor peaks and after cocaine (5 mg/kg) the duration of the secondary rise was prolonged. Cocaine had no effect on the action of nicotinamide.

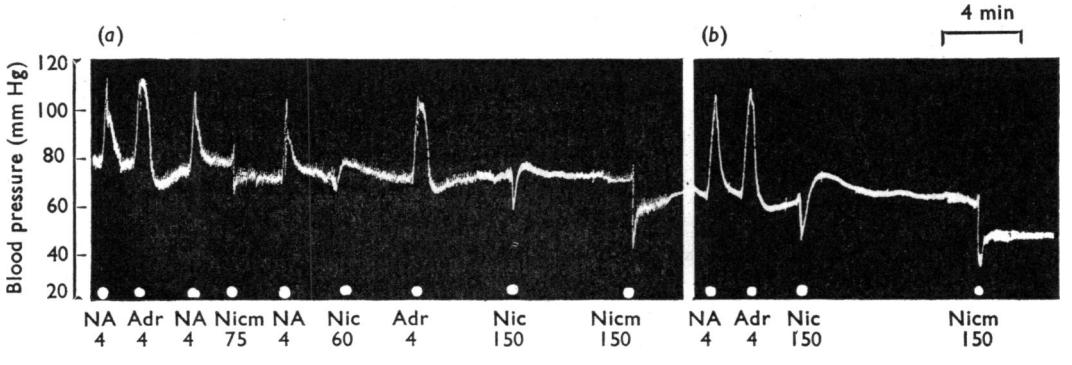

Fig. 4. Blood pressure of a rabbit (2 kg) anaesthetized with urethane. Noradrenaline (NA), adrenaline (Adr), nicotinic acid (Nic). (a) Before cocaine. (b) Thirty min after cocaine (2.5 mg/kg, intravenously). Cocaine potentiated the duration and intensity of the secondary pressor response to nicotinic acid. All doses in μg/kg, except for nicotinic acid and nicotinamide in mg/kg.

Effect of bretylium

In two rabbits, bretylium (8 to 10 mg/kg) blocked the secondary pressor response to nicotinic acid. Nicotinic acid (120 and 240 mg/kg) caused a primary fall followed by a secondary sustained rise in blood pressure. After bretylium, the action of adrenaline and noradrenaline was potentiated but nicotinic acid caused only a fall in blood pressure. The action of nicotinamide was not appreciably affected (Fig. 5).

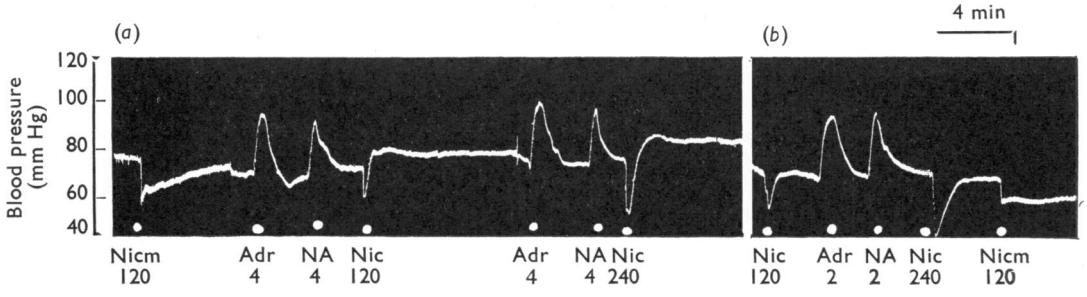

Fig. 5. Blood pressure of a rabbit (1.85 kg) anaesthetized with urethane. Nicotinamide (Nicm), adrenaline (Adr), noradrenaline (NA), nicotinic acid (Nic). Between (a) and (b) bretylium tosylate was injected (10 mg/kg). Time interval between (a) and (b) is 30 min. Note that nicotinic acid caused a fall in blood pressure followed by a sustained secondary rise but after bretylium, nicotinic acid caused only a fall in blood pressure. Doses in μg/kg, except for nicotinic acid and nicotinamide in mg/kg.

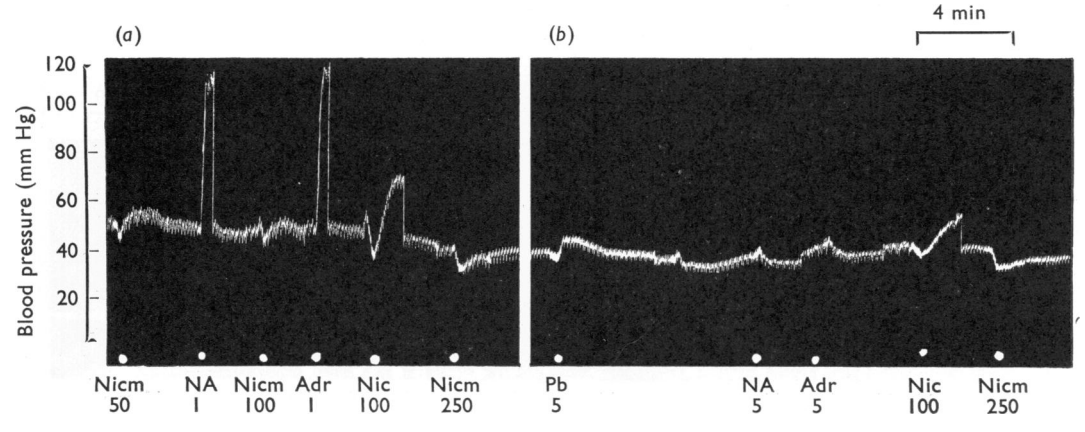

Fig. 6. Blood pressure of a reserpinized rabbit (2 kg) anaesthetized with urethane and treated 24 hr earlier with reserpine (5 mg/kg, intravenously). Nicotinamide (Nicm), noradrenaline (NA), adrenaline (Adr), nicotinic acid (Nic). In (b) phenoxybenzamine (2 mg/kg, intravenously). Note that phenoxybenzamine caused a slight pressor response ; in non-reserpinized rabbits it usually caused a significant sustained fall in blood pressure. Doses in μg/kg, except for nicotinic acid and nicotinamide in mg/kg.

Effect of reserpine

One rabbit was treated with reserpine (5 mg/kg, intravenously) and 24 hr later nicotinic acid (100 mg/kg) caused a transient rise and fall followed by an exaggerated secondary rise in blood pressure. However, a second injection of nicotinic acid (100 mg/kg) caused only a much reduced response compared with the effect of the first injection. Increasing the dose did not increase the response. Phenoxybenzamine (5 mg/kg) diminished the action of nicotinic acid. It was noted that phenoxybenzamine, which in normal rabbits caused a substantial sustained fall in blood pressure, caused a brief rise in blood pressure in reserpine-treated rabbits (Fig. 6). Reserpine rendered the rabbit relatively insensitive to the action of nicotinamide. Another reserpinized rabbit showed similar effects as the first rabbit.

Cats

In contrast to rabbits, nicotinic acid injection (200 to 600 mg/kg) into four cats resulted only in a fall in blood pressure. This fall started within 5 sec and lasted for about 1 min. A dose less than 200 mg/kg did not cause any appreciable change in blood pressure. Neither atropine (1 mg/kg) nor mepyramine (2 mg/kg) (Fig. 7) affected

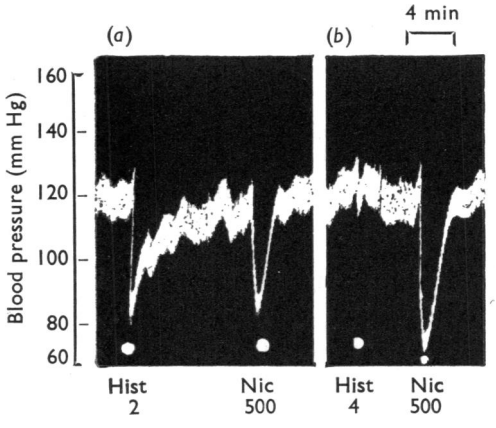

Fig. 7. Blood pressure of a cat (2 kg) anaesthetized with chloralose (80 mg/kg). Histamine (Hist), nicotinic acid (Nic). Between (a) and (b) mepyramine was injected (2 mg/kg, intravenously). Time interval between (a) and (b) is 15 min. Doses in μg/kg, except for nicotinic acid in mg/kg.

the action of nicotinic acid. As in the rabbit, nicotinamide (100 to 500 mg/kg) caused a sustained fall in blood pressure which, especially with large doses, did not return quite to control level even after 15 min. Mepyramine and atropine had no effect on the action of nicotinamide.

Dogs

In three dogs, nicotinic acid (100 and 375 mg/kg) caused a fall in blood pressure without any apparent pressor component and this agrees with the finding of Hauschild

(1960). As with rabbits and cats, nicotinamide (130 mg/kg) caused a sustained fall in blood pressure.

DISCUSSION

The action of intravenous injection of nicotinic acid on the blood pressure revealed species differences. The response in rabbits had one or more phases, but always had a pressor component. In cats and dogs, nicotinic acid caused only a fall in blood pressure which, together with the initial action of nicotinic acid in the rabbit, is most probably due to a peripheral action because it was not blocked by atropine or hexamethonium. These species differences in nicotinic acid action are most probably not due to differences in anaesthetics because the pressor responses to nicotinic acid were observed in rabbits anaesthetized with chloralose and in those anaesthetized with sodium barbitone. However, the route of nicotinic acid administration could be important in the species differences to nicotinic acid, being the jugular vein in rabbits and the femoral vein in cats and dogs. The response to nicotinamide in all three species was a sustained fall in blood pressure which was not affected by mepyramine, atropine or hexamethonium, and is most probably due to a peripheral action. Nicotinic acid and nicotinamide, intradermally injected into the rat, increase capillary permeability and this effect is not inhibited by atropine, phenoxybenzamine, mepyramine and/or bromolysergic acid diethylamide (Abdel-Aziz, unpublished).

The pressor component in the response to nicotinic acid in the rabbit usually started 15 to 90 sec after injection. This suggests that it is due to an indirect action and most probably mediated through the release of some pressor substance(s). It is known that histamine injection into the rabbit causes a pressor response (Krantz & Carr, 1961); this is confirmed in the present work. It was first thought that the pressor action of nicotinic acid might be mediated through the release of histamine. However, mepyramine in sufficient doses to block the action of large doses of histamine did not block the pressor action of nicotinic acid. Of interest is the finding that mepyramine in certain doses reversed the usual pressor response to histamine in the rabbit.

The other possibility in the mechanism of the pressor effect of nicotinic acid in the rabbit is that it might be mediated through the release of catecholamines, as produced by some pyridine compounds (Schoepke & Shideman, 1962). This possibility is supported by the observation that some sympathetic α-receptor blocking agents such as phenoxybenzamine and ergotamine almost completely blocked the pressor response. When rabbits were treated with bretylium, nicotinic acid caused only a fall in blood pressure, an effect possibly explained by the fact that bretylium reduces the release of catecholamines from their stores by reserpine at least in cats (Hertting, Axelrod & Patrick, 1962). On the other hand, hexamethonium potentiated this pressor response and hexamethonium is known to potentiate the action of catecholamines and that of substances which cause their release (Slater & Dresel, 1952; Trendelenburg, 1961; Staszeweska-Barczak & Vane, 1965). Also cocaine, which is known to block the uptake of catecholamines and to potentiate their effect (Macmillan, 1959; Whitby, Hertting & Axelrod, 1960), potentiated the pressor action of nicotinic acid in the rabbit.

The action of nicotinic acid after reserpine is difficult to interpret. In reserpinized rabbits the first injection of nicotinic acid usually resulted in an exaggerated response, but when the same or a larger dose was injected it caused only a very diminished effect. Reserpine depletes catecholamine stores and the exaggerated effect of the first dose of nicotinic acid might be due to the release of a labile residual minute amount of catecholamines after treatment with reserpine. The persistent, though much reduced, pressor action of nicotinic acid after reserpine might be due to a direct action on the heart.

It is not likely that the pressor action of nicotinic acid is mediated through a baroreceptor or chemoreceptor action because bilateral vagotomy and carotid sinus and body denervation did not diminish, but actually potentiated the action of nicotinic acid, probably by abolition of buffer reflex action. An effect on the vasomotor centre cannot be excluded as another contributing factor in the action of nicotinic acid. Further investigations are in progress to study the effect of nicotinic acid on the catecholamine level in blood of different species as well as its cardiovascular action after adrenal gland occlusion.

SUMMARY

1. The action of intravenous injection of nicotinic acid on the blood pressure of anaesthetized rabbits, cats and dogs revealed species differences. In some rabbits nicotinic acid caused only a sustained pressor response while in most rabbits this pressor response was preceded either by a transient fall or by a transient rise. On the other hand in cats and dogs nicotinic acid caused only a fall in blood pressure.

2. Intravenous injection of nicotinamide caused a fall in blood pressure in rabbits, cats and dogs. This fall in blood pressure and that caused by nicotinic acid are most probably due to a peripheral action.

3. The mechanism of the sustained pressor component in the action of nicotinic acid in the rabbit was investigated. Histamine has been excluded as a mediator in this response as mepyramine did not affect it.

4. Hexamethonium, cocaine and carotid sinus and body denervation with vagotomy potentiated the pressor response but it was blocked by bretylium and phenoxybenzamine.

5. It is concluded that the pressor response caused by nicotinic acid in the rabbit is probably mediated through the release of catecholamines.

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