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Influence of nicotine on the coronary circulation of the isolated heart of the cat

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Nicotine administered to the isolated perfused heart of the cat produces initial bradycardia followed by long-lasting tachycardia and enhancement of the strength of contractions. The coronary flow after a reduction shows a prolonged increase that continues after the heart hyperactivity has ceased. When nicotine was given after hexamethonium or after reserpine pretreatment, the cardio-stimulation disappeared and only reduction of the coronary flow was obtained. It is concluded that the complexity of the pharmacological effect of nicotine on the coronary flow of the isolated heart preparation depends on an indirect vasodilator action mediated by the heart stimulation due to liberation of intracardiac catecholamines and also on vasoconstriction due to a direct effect of the drug on the coronary vasculature.

IT has been postulated that the vasodilator effect of catecholamines on the coronary circulation is secondary to the myocardial stimulating action and that the arteriolar smooth muscle responses are due to the increased myocardial metabolism (Berne, 1958; Douglas, Armengol & Talesnik, 1960). The vasodilatation is preceded by a transient phase of diminution of the coronary flow that has been ascribed to a direct action of the catecholamines on the coronary vessels (Berne, 1958; Hardin, Scott & Haddy, 1961).

According to Ahlquist (1948), the effect of catecholamines depends on two types of adrenaline receptors: (1) α-receptors, responsible for the vasoconstriction, and (2) β-receptors, responsible for the myocardial stimulation (tachycardia and increase in the force of contraction) as well as for the coronary vasodilatation; but Ahlquist did not comment on whether the coronary vasodilatation was a primary or a secondary effect. However it has been demonstrated on the isolated dog heart, arrested with potassium chloride, that isoprenaline produces coronary vasodilatation in the absence of cardiac stimulation. This response can be abolished by blocking the β-receptors with pronethalol (Klocke, Kaiser, Ross & Braunwald, 1965). These results indicate that the vasodilatation may be a primary action of catecholamines.

Nicotine produces myocardial stimulation similar to that obtained with adrenaline or noradrenaline (Hoffmann, Hoffmann, Middleton & Talesnik, 1945; Burn, 1960) and apparently this action depends on the intracardiac liberation of catecholamines (Hoffmann & others, 1945). The changes in the coronary flow observed with nicotine have been very divergent. Thus it has been reported that nicotine increases the coronary flow (Travell, Rinzler & Karp, 1960; Bellet, West, Müller & Manzoli, 1962), that it reduces it (Leaders & Long, 1962; Kareva, 1963) or that it does not alter it (Regan, Frank & others, 1961). The complexity of the pharmacological action of nicotine (Burn, 1960; Comroe, 1960), as well as the difficulty in obtaining comparable data from investigations made under different experimental conditions, are some of the factors involved in this problem.

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Nevertheless the effects of nicotine on coronary flow have been ascribed to the liberation of catecholamines (Travell & others, 1960).

The present study has been undertaken on the isolated cat heart in an attempt to elucidate the precise nature of the mode of action of nicotine on the coronary vasomotor tone.

Methods

Sixteen experiments were made on the isolated cat heart preparation perfused according to Langendorff's method as described by Douglas & others (1960). The perfusion fluid used was Tyrode solution oxygenated with a mixture of oxygen 95% and carbon dioxide 5%, at 38° and a constant perfusion pressure of approximately 40 mm Hg. The frequency and amplitude of the ventricular contractions and the coronary flow were registered continuously on smoked paper. The flowmeters were of the rheograph type described by Douglas & others (1960). Since the records of the inflow and the outflow from the coronary vessels were very similar the latter have been omitted in the figures shown.

Single doses of nicotine (sulphate) and noradrenaline (Levofed, Winthrop) were administered through the aortic cannula in a constant volume of 0·1 ml. Prolonged administration of hexamethonium (C_6), nicotine and atropine (Bellafolina, Sandoz) was carried out with a slow injection pump (0·8 ml/min).

Four cats were pretreated 24 hr before the experiment with reserpine (Serpasil, Ciba) by subcutaneous injection of 4 mg/kg body weight.

Results

EFFECT OF SINGLE INJECTIONS OF NICOTINE

The administration of 5 μg or more of nicotine produced, after 1 to 5 sec, bradycardia lasting from 10 to 15 sec; with the larger doses there was an initial cardiac arrest. After the period of bradycardia a long lasting

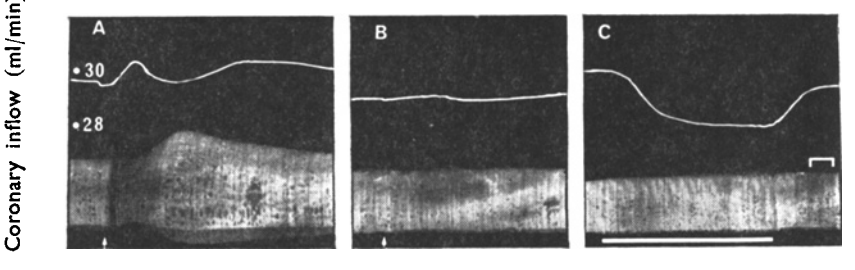

FIG. 1. A. Effect of single injections of nicotine (20 μg at arrow). Early cardio-inhibition is followed by prolonged cardio-stimulation. Between (A) and (B), perfusion with hexamethonium (1 mg/min). B. Effect of single injection of nicotine (20 μg at arrow) after hexamethonium. Both cardio-inhibition and cardio-stimulation are suppressed. The effect on the coronary inflow, observed in (A), does not occur. C. Prolonged administration of nicotine after hexamethonium. Although the ventricular contraction remains unaltered, a sustained reduction of the coronary inflow can be observed during nicotine infusion. Time scale: 10 sec.

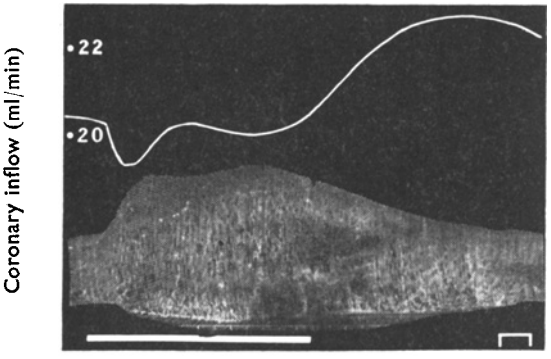

FIG. 2. Effect of the prolonged injection of nicotine (200 μg/70 sec at bar). The early cardio-inhibitor effect was abolished by atropine. The coronary inflow increases at the end of the nicotine infusion. Time scale: 10 sec.

tachycardia and increase in the amplitude of the contractions occurred. This phase of the nicotine effect could be observed for 60 to 120 sec (Fig. 1A). During these changes in heart activity (an expression of the product of heart rate and amplitude of the ventricular contractions), changes in the coronary flow were also observed. During the phase of bradycardia there was an increase in the coronary flow. When the period of myocardial stimulation (tachycardia and increased force of contraction) began, the coronary flow diminished, but later, when the myocardial stimulation had become maximal, the coronary flow increased again and remained raised long after myocardial stimulation was over (Fig. 1A).

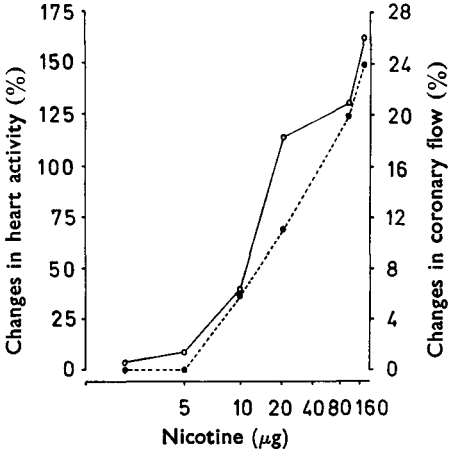

FIG. 3. Relationship between nicotine dosage, heart activity (○) and coronary flow (●). Heart activity has been defined as the product of heart rate and amplitude of the ventricular contractions.

Nicotine (50 to 200 μg) given over 45 to 70 sec (Fig. 2) produced tachycardia and increase in the amplitude of the contractions by 80 to 160% of the initial values. The early phase of bradycardia was abolished by previous administration of atropine (0·5 mg slowly injected in 15 min). If nicotine was then given, the coronary flow was slightly reduced while myocardial stimulation reached its maximal level. When the nicotine injection was stopped, a rapid increase of the coronary flow was observed. This long-lasting effect persisted for 1 to 2 min after the myocardial activity had returned to normal.

The total coronary flow increased by 6 to 24% after single injections or prolonged administration of nicotine, depending on the degree of myocardial stimulation evoked by the different doses (Fig. 3).

Perfusion with hexamethonium (1 mg/min) abolished both the initial bradycardia and the myocardial stimulation induced by single injections of 10 to 200 μg of nicotine (Fig. 1B). The coronary flow usually did not change or was slightly reduced (by not more than 5%) for a short time (Fig. 1 B).

Slow infusions over 40–70 sec of nicotine in amounts of 200 to 1,000 μg produced a reduction of the coronary flow by 5 to 25% depending on the dose used. The diminution of the coronary flow appeared 1 to 5 sec after the nicotine infusion began (Fig. 1C). When nicotine administration ceased, the coronary flow recovered quickly, reaching its initial level in about 30 to 40 sec. When slow injections of higher doses of nicotine (total dose of 500 μg or more) were used, a slight increase in the amplitude of the contractions sometimes appeared but the coronary flow showed the same pattern of reduction.

It seemed possible that increased myocardial activity, by increasing the extravascular support to the coronary vessels, might itself increase the impedance to coronary flow and thus mask any direct action of nicotine on the vessels. We therefore repeated these experiments on hearts treated with hexamethonium and caused to fibrillate by electrical stimulation (Figs 4A and B). Under these conditions nicotine (1 mg infused

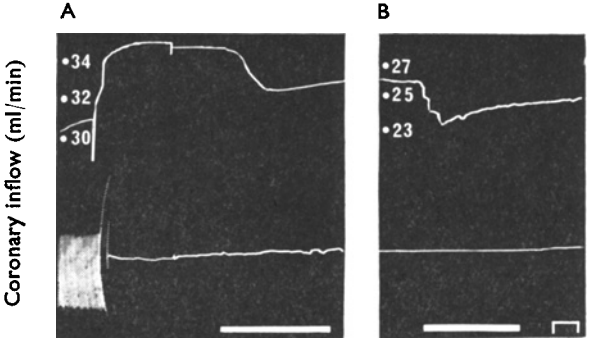

FIG. 4. Effect of nicotine after hexamethonium in electrically induced ventricular fibrillation. A. When fibrillation starts there is an increase in the coronary inflow. Prolonged injection of nicotine reduces the coronary inflow. B. The same response at a lower level of coronary inflow. In (A) nicotine 1 mg/40 sec at bar. In (B) nicotine 1 mg/35 sec at bar. Time scale: 10 sec.

over 35–40 sec) induced a similar but slightly smaller diminution of coronary flow.

EFFECT OF NICOTINE AFTER PRE-TREATMENT WITH RESERPINE

In the hearts from 4 animals previously treated with reserpine, both single and prolonged injections of nicotine produced initial bradycardia which was abolished by atropine (Fig. 5A and B). With single doses of

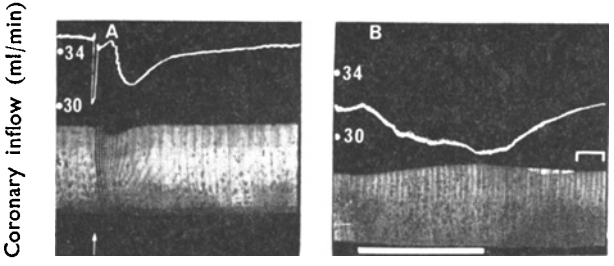

FIG. 5. Effect of nicotine after reserpine pre-treatment. A. Cardio-inhibition is produced by a single injection of nicotine (50 μg at arrow) without cardio-stimulation. Reduction of the coronary flow occurs. Between (A) and (B) atropine was administered. B. Prolonged injection of nicotine (1 mg/45 sec at bar) after atropine produces only a reduction of the coronary inflow during the nicotine infusion. Time scale: 10 sec.

50 μg of nicotine it was possible to observe a reduction of the coronary flow in the absence of any myocardial stimulation (Fig. 5A). Prolonged injections of a total dose of 100 to 1,000 μg of nicotine during 45 to 70 sec produced a reduction of the coronary flow of 10 to 25%; very high doses also caused a slight increase in the amplitude of the ventricular contractions (10%) (Fig. 5B).

Discussion

The action of nicotine in stimulating the synapses of both sympathetic and parasympathetic ganglia is well known. In the isolated heart, stimulation of the vagal synapses is most probably responsible for the initial bradycardia that follows the administration of nicotine (Perry & Talesnik, 1953). There is strong evidence that nicotine also causes a release of catecholamines when administered to the isolated heart (Hoffmann & others, 1945; Burn & Rand, 1958). The site of action of the catecholamines is by no means clear, although the existence of sympathetic ganglia or chromaffin tissue in the heart has been postulated (Hoffmann & others, 1945; Burn, 1960) and is supported by experiments claiming that stimulation of pre-ganglionic sympathetic fibres with synapses situated in the heart was possible (Nagy & Szentivangi, 1961). Furthermore acetylcholine can induce catecholamine liberation from the heart.

As shown in Fig. 3 the degree of coronary vasodilatation produced by nicotine is related to the degree of myocardial stimulation evoked. This confirms the results of previous workers (Travell & others, 1960; Bellet & others, 1960).

It has been suggested however that nicotine has direct coronary vasoconstrictor properties also mediated by an adrenergic mechanism (Leaders & Long, 1962; Kareva, 1963). The problem is still more difficult to analyse if one considers the recently demonstrated fact that the response of isolated and perfused strips of coronary smooth muscles and arteriolar segments to catecholamines is variable according to the diameter of the vessel. The smaller arterioles are relaxed by noradrenaline while the larger vessels (over 1·7 mm in diameter) are constricted with lower doses. These differences have been attributed to a quantitative difference in distribution of the α- and β-receptors (Zuberbuhler & Bohr, 1965). Therefore, considering only the isolated heart, the gross effect of nicotine on the total coronary flow would be the resultant of its main action in addition to a number of others of varying predominance, all of which might interact.

The use of hexamethonium allows the reaction of the coronary vessels to nicotine to be studied in the absence of bradycardia and of subsequent myocardial stimulation. The bradycardia is almost certainly suppressed by the blocking action of hexamethonium at the vagal intracardiac synapses (Perry & Talesnik, 1953). The doses of hexamethonium used were large enough to ensure that the vagal ganglionic cells were adequately blocked (Perry & Talesnik, 1953; Middleton, Oberti, Prager & Middleton, 1956; Leaders & Long, 1962; Kareva, 1963). The myocardial stimulation is reduced or abolished by an inhibition of the discharge of catecholamines by some mechanism not yet well understood (Burn, 1960; Burn & Gibbons, 1964).

There is a significant difference in the action of high doses of nicotine on the coronary flow before and after the administration of hexamethonium. A high dose of nicotine produced a substantial reduction in the total coronary flow in heart treated with hexamethonium (Fig. 1C) despite the lack of any myocardial stimulation, suggesting that the changes in coronary flow are not due to gross modifications of the extravascular support. Thus it is quite possible that the reduction of the coronary flow under these conditions is due to a direct vasoconstrictor action. Furthermore, after pre-treatment of the animals with reserpine, which depletes the catecholamine stores (Burn & Rand, 1958), nicotine acts on the coronary bed by producing direct vasoconstriction as it does in the experiments with hexamethonium.

Accordingly it is clear that the overall effect of nicotine on coronary tone in the isolated heart depends on a combination of several different mechanisms of action. When nicotine produces increased heart activity and an associated liberation of catecholamines the main effect is a vasodilatation, described as a servo-mechanism of coronary adaptation by Douglas & others (1960) and Douglas & Talesnik (1960). This secondary vasodilatation competes with a direct vasoconstrictor effect that can be unmasked when the influence of the catecholamines is suppressed. It is relevant to emphasize the importance of the servo-mechanism of coronary adaptation since in the rabbit with experimental atherosclerosis, which physically impairs the vasodilatation, nicotine elicits only vasoconstriction

(Travell & others, 1960). Furthermore, in the fibrillating heart (Fig. 4A and B) treated with hexamethonium, nicotine still elicits vasoconstriction, and it seems clear that this effect must be a direct one upon the coronary vessels. The vasoconstrictor effect of nicotine is smaller when the heart is fibrillating and this may well be due to the fact that fibrillation alone is known to cause an increase in coronary flow (Douglas & others, 1960).

Apart from these major effects of nicotine, there remain to be explained the two transient initial effects observed. The first is the initial increase in coronary flow seen after nicotine is given in hearts not perfused with hexamethonium or atropine (Fig. 1A). This seems certain to be related to the bradycardia evoked by nicotine since the reduction of the extravascular coronary impedance (extravascular "support"; Katz, Jochim & Bohning, 1938) under bradycardia or cardiac arrest has already been pointed out as responsible for this effect (Douglas & others, 1960; Leaders & Long, 1962).

The second is the diminution of the coronary flow that follows the short initial increase (Figs 1A and 2). This also seems to depend on a change in the extravascular impedance (extravascular "support"), in this case an increase due to the myocardial stimulation (Douglas & others, 1960; Travell & others, 1960; Leaders & Long, 1962).

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