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VASOCONSTRICTOR ACTION OF TOLAZOLINE

BY

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In cats treated with reserpine and anaesthetized with pentobarbitone sodium the adrenergic blocking drug, tolazoline, caused a rise of arterial pressure which was inhibited by previous administration of phenoxybenzamine. Tolazoline increased the contractions of the isolated papillary muscles of normal cats but not of cats treated with reserpine. Intra-arterial injection of tolazoline into dogs treated with reserpine and anaesthetized with pentobarbitone sodium reduced the blood flow in the coeliac artery. It is considered that, following reserpine, tolazoline has a sympathomimetic vasoconstrictor action.

We have previously found that the adrenergic blocking drug, tolazoline, has a pressor action in dogs treated with reserpine which is inhibited by phenoxybenzamine, and we have concluded that tolazoline may have a sympathomimetic vasoconstrictor action (Benfey & Varma, 1963a). Ahlquist, Huggins & Woodbury (1947) reported that the pressor effect of tolazoline represents the algebraic sum of its vasodilator effect tending to lower the blood pressure and an increase in cardiac output tending to raise it. Accordingly one would expect that the pressor effect of tolazoline would be absent if previous treatment with dichloroisoprenaline prevented the effect on the heart. Furthermore, the positive inotropic effect should occur both in normal hearts and in hearts treated with reserpine, and vasoconstriction should not be demonstrable. This paper describes an investigation of the mechanism of the pressor effect of tolazoline on these premises. The results confirm our previous conclusion that tolazoline has a sympathomimetic vasoconstrictor effect.

METHODS

Cats were anaesthetized with pentobarbitone sodium (30 mg/kg, intraperitoneally). Animals previously treated with reserpine received smaller amounts of the anaesthetic. The lungs were ventilated with a Harvard pump. The contractile force of the heart was measured with a Walton strain gauge arch attached to the right ventricle, the femoral arterial blood pressure with a Sanborn pressure transducer, and the heart rate from an electrocardiograph. A Sanborn 150 recorder was used.

Papillary muscles from the right ventricles of cats anaesthetized with ether were suspended in Tyrode solution at 38° C through which was bubbled a mixture of 5% carbon dioxide and 95% oxygen. The muscles were stimulated by rectangular pulses of 2 msec duration and supramaximal intensity at a frequency of 1 shock/sec. The contractions were recorded on a kymograph.

Dogs were anaesthetized with pentobarbitone sodium (30 mg/kg or less, intravenously). The carotid arterial blood pressure was measured and recorded as in cats. In addition a

Shipley-Wilson rotameter (range 0 to 200 ml./min) inserted into the coeliac artery was used to determine blood flow and cannulation of a small artery distal to the rotameter permitted intra-arterial injections.

Reserpine (Serpasil, Ciba, 1 mg/kg) was injected intraperitoneally on the day before the experiment. Dichloroisoprenaline (Eli Lilly, 5 mg/kg) and phenoxybenzamine (Dibenzyline, Smith, Kline & French, 5 mg/kg) were injected intravenously 30 min before administration of tolazoline. We have previously found (Benfey & Varma, 1963b) that, in cats treated with reserpine and anaesthetized with pentobarbitone sodium, 5 mg/kg of phenoxybenzamine, injected 30 min before, converts the pressor effect of adrenaline (1 μg) into a depressor effect, while 5 mg/kg of dichloroisoprenaline, injected 30 min earlier, potentiates the pressor effect of adrenaline and converts the depressor effect of isoprenaline (1 μg) into a small pressor effect. In addition, we have found that under these conditions both phenoxybenzamine and dichloroisoprenaline inhibit enhancement of the cardiac contractile force by noradrenaline, adrenaline and isoprenaline.

Tolazoline (Priscoline, Ciba), hydergine (Sandoz), piperoxan (Benzodioxane, Poulenc), (−)-noradrenaline bitartrate monohydrate and (−)-isoprenaline bitartrate dihydrate were injected into a femoral vein in cats and an external jugular vein in dogs unless otherwise stated. Drugs were made up in 0.9% (w/v) saline.

RESULTS

The effects of tolazoline on arterial blood pressure, cardiac contractile force and heart rate of anaesthetized cats are shown in Fig. 1. Tolazoline raised the blood pressure and slightly increased cardiac contractile force. The pressor effect of tolazoline was not significantly altered by previous treatment with reserpine or with reserpine and dichloroisoprenaline, but was inhibited by reserpine together with phenoxybenzamine. The effect of tolazoline on the force of cardiac contraction was enhanced by reserpine but was inhibited both by dichloroisoprenaline and by phenoxybenzamine. It is thus evident that, in cats treated with reserpine and dichloroisoprenaline, tolazoline raised the blood pressure without increasing cardiac contractile force or heart rate.

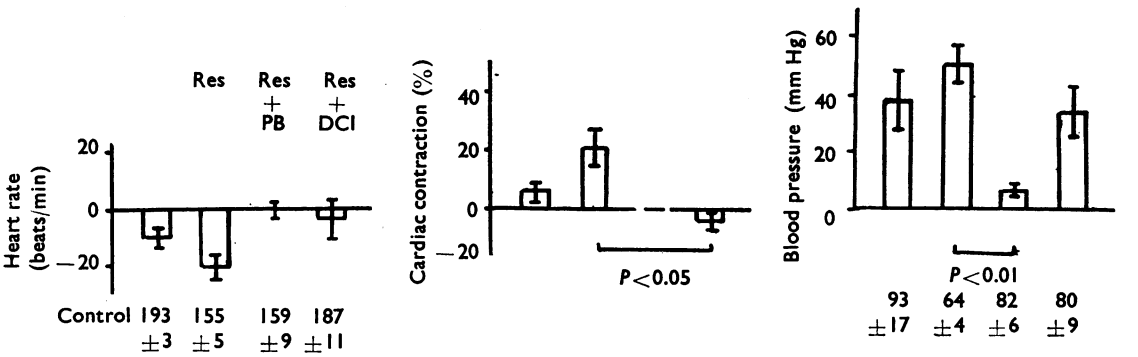

Fig. 1. Effects of tolazoline (0.5 mg/kg, intravenously) on heart rate, force of cardiac contraction and mean arterial blood pressure of cats anaesthetized with pentobarbitone sodium. All ordinates refer to changes in parameters from the controls. The vertical bars represent standard errors of the means. Res, reserpine (1 mg/kg, injected intraperitoneally on the day before the experiment); PB, phenoxybenzamine (5 mg/kg), and DCI, dichloroisoprenaline (5 mg/kg), injected intravenously 30 min before the tolazoline. There were four groups of five cats, corresponding to the four columns of each histogram.

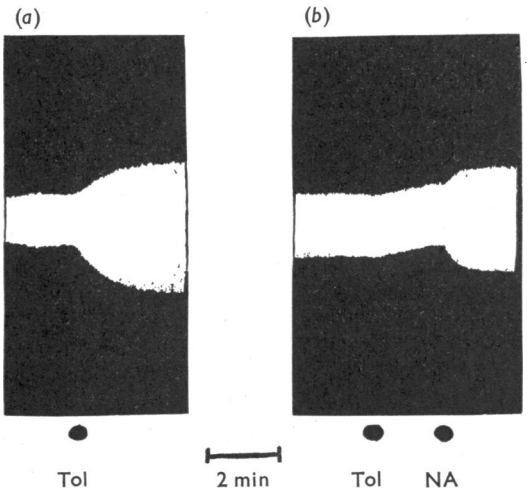

Fig. 2. Effects of tolazoline (Tol, 50 μg/ml.) and noradrenaline (NA, 10 ng/ml.) on the force of contraction of cat isolated papillary muscles. (*a*), preparation from a normal cat; (*b*), from a cat treated with reserpine.

The cat papillary muscle was used to study the action of toazoline on isolated heart tissue. Fig. 2 shows that tolazoline (50 μg/ml.) increased the contractions of the preparation made from nontreated cats but had no effect on the preparation made from cats treated with reserpine. Stimulation of the papillary muscle by tolazoline and absence of this effect in muscles from animals treated with reserpine was a consistent finding in a total of sixteen hearts.

Typical responses to sympathomimetic drugs of the coeliac vascular bed of a dog treated with reserpine are seen in Fig. 3. Intra-arterial injection of noradrenaline reduced arterial blood flow, whilst isoprenaline increased it. However, with injec-

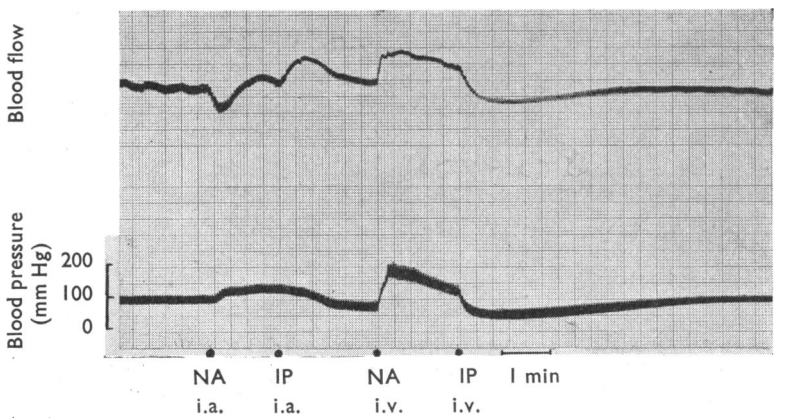

Fig. 3. Effects of noradrenaline (NA, 1 μg/kg) and isoprenaline (IP, 1 μg/kg), injected into the coeliac artery (i.a.) and jugular vein (i.v.) of a dog anaesthetized with pentobarbitone sodium and treated with reserpine 1 day before, on coeliac arterial blood flow (upper trace) and systemic arterial blood pressure (lower trace).

tions into the jugular vein, the flow in the coeliac artery passively followed the changes in systemic blood pressure, being increased by a rise in pressure (noradrenaline) and reduced by a fall (isoprenaline). The effect of injection of tolazoline into the coeliac artery on arterial blood flow was studied in anaesthetized dogs treated with reserpine. Tolazoline was used in an amount sufficient to raise systemic arterial blood pressure. Fig. 4 shows that the long-lasting pressor effect of tolazoline (0.5 mg/kg) was associated with a reduction in coeliac arterial blood flow. This result was obtained in each of three animals studied. Tolazoline, like hydergine (0.1 mg/kg), increased the flow in the femoral artery.

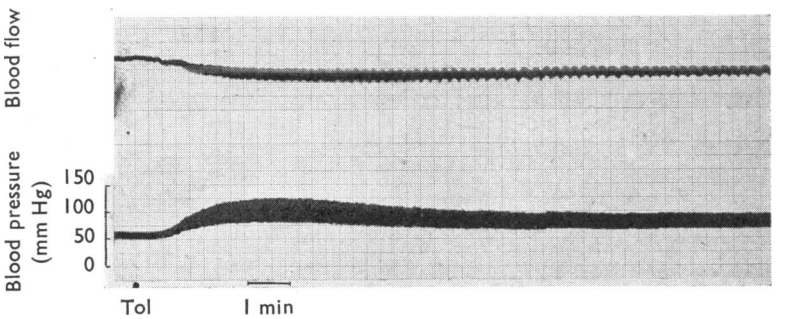

Fig. 4. Effects of tolazoline (Tol, 0.5 mg/kg), injected into the coeliac artery of a dog anaesthetized with pentobarbitone sodium and treated with reserpine, on coeliac arterial blood flow (upper trace) and systemic arterial blood pressure (lower trace). The blood flow was recorded under conditions similar to those of Fig. 3.

The adrenergic blocking drugs, piperoxan (Jourdan, 1935), hydergine (Konzett & Rothlin, 1953) and phenoxybenzamine (Benfey, 1961), which have a pressor effect in animals treated with ganglion blocking drugs or by section of the cervical spinal cord, were studied for comparison. Reductions in coeliac blood flow associated with prolonged rises in systemic blood pressure of anaesthetized dogs treated with reserpine were observed following intra-arterial injection of piperoxan (5 mg/kg), hydergine (0.1 mg/kg) and phenoxybenzamine (10 mg/kg).

The drugs did not reduce coeliac blood flow 15 to 30 min after an adrenergic blocking drug had been injected intra-arterially. The second intra-arterial administration of an adrenergic blocking drug generally increased blood flow and had little or no systemic pressor effect.

DISCUSSION

Tolazoline is known as a vasodilator agent. Johnson, Green & Lanier (1953) found that it had a vasodilator effect in the hind-leg of the dog. In their studies on the effects of tolazoline in dogs injected with morphine and anaesthetized with ether or pentobarbitone sodium, Ahlquist *et al.* (1947) used doses of 1 to 10 mg/kg and found that a pressor effect usually occurred with the larger doses. However, there was peripheral vasodilation in all dogs, even in those showing a pressor response. Tolazoline (10 mg/kg) greatly increased cardiac output, and results on dog isolated perfused hearts indicated that this was a sympathomimetic effect. The authors

concluded that the changes of blood pressure caused by tolazoline represent the algebraic summation of its two diverse effects.

We used a small dose of tolazoline (0.5 mg/kg) after administration of reserpine. Under these conditions the pressor effect appears to be due to sympathomimetic vasoconstriction since phenoxybenzamine prevented it and inhibition of cardiac stimulation by dichloroisoprenaline did not. Thus, following reserpine, tolazoline appears to behave like the related hypertensive imidazolines. Presumably the vasoconstrictor action of tolazoline is so weak that in the presence of normal sympathetic tone the blockade of the vasoconstrictor receptors leads to a fall in blood pressure. Tolazoline may be a "partial sympathomimetic agonist", rather than a true adrenaline antagonist, with a low activity and a high affinity for vasoconstrictor receptors. If so, the sympathomimetic action of the drug would be most clearly manifest when the sympathetic tone is low.

West & Dille (1953) found that, while dihydroergotamine increased the flow in the femoral artery of the dog, it reduced it in the anterior mesenteric artery. Our results again demonstrate the difference in the responsiveness of different vascular beds to the same drug, since both tolazoline and hydergine increased the flow in the femoral artery and reduced it in the coeliac artery in the dog treated with reserpine.

The increase in cardiac contractile force following tolazoline in anaesthetized cats treated with reserpine appears to be secondary to the rise in blood pressure, as the same effect was noted following hydergine in anaesthetized dogs (Benfey & Varma, 1963a) and cats previously treated with reserpine. However hydergine did not increase the contractions of the isolated papillary muscle of normal cats or of those treated with reserpine. The inability of tolazoline to increase the contractions of papillary muscles from cats treated with reserpine further supports the conclusions that in animals treated with reserpine the pressor response to tolazoline is due to direct vasoconstriction and that the increase in cardiac contractile force is secondary. It is possible that the stimulation of the isolated papillary muscle from nontreated cats is mediated by the release of endogenous catechol amines.

The observation that, following reserpine, tolazoline had no effect on the papillary muscle but remained active on the blood pressure is reminiscent of the action of dopamine. Bejrablaya, Burn & Walker (1958) found that the pressor effect of dopamine was greater in cats treated with reserpine than in normal cats, while the chronotropic effect of the drug was smaller in heart-lung preparations of dogs treated with reserpine than in those of nontreated dogs.

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