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SYMPATHETIC β-RECEPTOR BLOCKING ACTION OF METHOXAMINE

BY

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Since Barger & Dale (1910) investigated the mechanism of action of sympathomimetic amines, much work has been done to determine the different actions of these compounds. Though most of these amines imitate the effects of stimulation of sympathetic nerves, some also possess properties of a different variety. For example, Finkleman (1930) demonstrated that ephedrine abolished the relaxing effect of adrenaline on the rabbit isolated ileum; Aström (1948, 1949) showed that (−)-*N*-ethyl ephedrine as well as fifteen other members of the phenylethylamine series blocked the inhibitory action of adrenaline; Ahlquist, Huggins & Woodbury (1947) reported that ephedrine modified the actions of adrenaline and isoprenaline on the blood pressure of cats, and Neidle, Gruber & Copeland (1951) noted that some sympathomimetic amines blocked the bronchodilator action of adrenaline. The present investigation concerns methoxamine, used in clinical practice as a pressor amine during surgical and spinal anaesthesia (Hjort, Randall & de Beer, 1948; Stutzman, Pettinga & Fruggiero, 1949; Lahti, Brill & McCawley, 1955). These workers have emphasized that the pressor effect of this drug is accompanied by a powerful bradycardia. The cardiac slowing action of methoxamine has been utilized in cases of supraventricular tachycardia (Nathason & Miller, 1952; Solomon, 1954; Berger & Rackliffe, 1953).

According to Aviado & Wnuck (1957) the reduction in heart rate produced by methoxamine in dogs is due to a stimulation of the carotid sinus and aortic arch reflexes, initiated by the vasoconstriction and resultant rise in blood pressure.

METHODS

Experiment with cats. Cats of either sex, weighing between 1.8 and 4.2 kg, were anaesthetized with ether followed by chloralose (80 mg/kg, intravenously). The blood pressure was recorded from a cannulated femoral artery by a mercury manometer. Drugs were injected into a femoral vein. Heart rates were recorded by the method of Daly & Schweitzer (1950). In female cats uterine motility was recorded with a frontal-writing lever of 10 : 1 magnification, with 2-g load on the muscle and attached by a string to one horn of the uterus. The carotid sinus was denervated by cutting the fibres between the sinus and the carotid body and was checked by the response to carotid clamping. The aortic arch was denervated by bilateral mid-cervical vagotomy which included the superior laryngeal branch of each vagus nerve. Acute cardiac sympathetic denervation was performed by removal of the sympathetic chain from the stellate ganglion to the level of T5 in open-chest animals during artificial ventilation. In some experiments the postganglionic cardiosympathetic nerves on the right side were stimulated with rectangular pulses of 1 msec duration at a frequency of 20 shocks/sec and at 4 V. Some cats were given reserpine (2 mg/kg, intraperitoneally) 24 hr before the experiment.

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Experiments with rabbit isolated auricles and rat heart preparations. Auricles from freshly killed rabbits weighing 1.5 to 2.0 kg were suspended as described by Burn (1952) in a 20-ml. organ-bath at 29° C. Ringer-Locke solution of the following composition (g/l.) was used: NaCl 9.0, D-glucose 1, $NaHCO_3$ 0.5, KCl 0.42 and $CaCl_2$ 0.18. The contractions were recorded with a spring lever of 12 : 1 magnification.

Rat hearts were perfused with Ringer-Locke solution by the method of Langendorff as described by Gunn (1913). The contractions were recorded with a spring lever of 12 : 1 magnification and the rate of beat was recorded by means of a Thorp impulse counter.

Experiments with rabbit isolated ileum preparation. Segments of rabbit ileum were suspended in a 10-ml. organ-bath of Tyrode solution of the following composition (g/l.): NaCl 8.0, $NaHCO_3$ 1.0, D-glucose 1.0, NaH_2PO_4 0.05, $MgCl_2$ 0.04, KCl 0.2 and $CaCl_2$ 0.15. The bath temperature was kept constant at 32° C. Records were made with a frontal-writing lever of 8 : 1 magnification with a 3-g load on the muscle, and when used methoxamine and phentolamine were incorporated in the Tyrode solution in the reservoir.

In all the isolated organ experiments, the bath (and reservoir) were gassed with oxygen.

Drugs. (−)-Adrenaline acid tartrate B.P. (Burroughs Wellcome), (±)-isoprenaline hydrochloride (Ward Blenkinsop), (−)-noradrenaline bitartrate (Levophed, Bayer Products) and methoxamine hydrochloride (Burroughs Wellcome) were used. Doses of these drugs are given in terms of the bases. Phenoxybenzamine (Dibenyline, Smith Kline & French) was dissolved in 5% ascorbic acid solution as a 10 mg/ml. solution. Reserpine (Serpasil, Ciba) was made up as a 5 mg/ml. solution in 20% ascorbic acid solution. Injections were intravenous unless otherwise stated.

RESULTS

Direct effects of methoxamine on the blood pressure and heart rate of cats. In cats anaesthetized with chloralose, methoxamine (0.5 mg/kg) produced an immediate rise in blood pressure which lasted for 15 to 35 min (eight experiments). The pressor response was always accompanied by a slowing of the heart which persisted after the blood pressure had returned to resting level (Table 1). Bilateral vagotomy and carotid sinus denervation reduced the slowing of the heart induced by methoxamine but did not abolish it. Thus in four experiments methoxamine (0.5 mg/kg) reduced the heart rate by 36%; after denervation of the carotid sinuses and aortic arch the same dose of methoxamine reduced the rate of the heart by 26%. Similar results were obtained in cats in which the pressor effect of methoxamine had been abolished by treatment with phenoxybenzamine (10 mg/kg) (Table 1).

In cats in which acute cardiac sympathetic denervation had been carried out in addition to carotid sinus and aortic arch denervation (four experiments) or treatment with phenoxybenzamine (four experiments), the reduction in heart rate produced by methoxamine was about 3% (Fig. 1). Similar results were obtained in cats treated with reserpine and given phenoxybenzamine (10 mg/kg). The results of these experiments are given in Table 1.

Thus neither the denervation of carotid sinuses and of the aortic arch nor administration of phenoxybenzamine prevented the bradycardia produced by methoxamine. Only additional removal of sympathetic tone to the heart either by cutting the sympathetic nerves or by treatment with reserpine did so. These results suggested that the reduction of the heart rate produced by methoxamine might be due to blocking the effects of endogenously released noradrenaline at the postganglionic sympathetic nerve endings. The following experiments were designed to test this hypothesis.

Effect of methoxamine on the increase in heart rate produced by sympathomimetic amines and by sympathetic nerve stimulation. The cardioacceleration produced by intravenous

TABLE 1

EFFECT OF INTRAVENOUS INJECTIONS OF 0·5 mg/kg OF METHOXAMINE ON THE HEART RATE OF CATS

Afferent denervation refers to denervation of the carotid sinuses and aortic arch, efferent denervation to cardiac sympathetic denervation. Dose of phenoxybenzamine, 10 mg/kg; of reserpine, 2 mg/kg. Duration of heart rate effect refers to the time interval between the injection of methoxamine and the return of heart rate to control level

		Action of methoxamine on						
		Blood pressure			Heart rate			
No. of cats	Condition	Control (mm Hg)	Maximum rise (mm Hg)	Duration of rise (min)	Control (per min)	Minimum after methoxamine (per min)	Change (%)	Duration (min)
4	None	135	85	25	172	110	36·0	105
	Afferent denervation	150	80	23	188	139	26·0	95
	Afferent and efferent denervation	110	82	26	152	148	3·0	65
4	None	140	78	30	168	108	36·0	90
	Phenoxybenzamine	85	0	0	172	131	24·0	75
	Phenoxybenzamine and efferent denervation	80	0	0	150	148	1·0	70
2	Reserpine and phenoxybenzamine	70	0	0	120	120	0·0	0

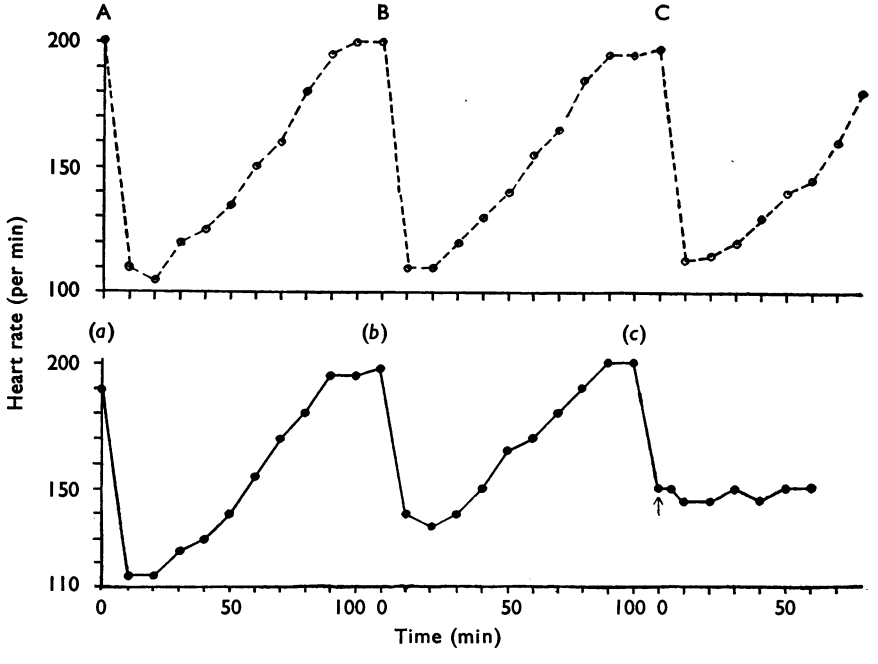

Fig. 1. Effect of methoxamine (0.5 mg/kg) on the heart rate of cats anaesthetized with chloralose. Upper record: control experiment showing that the slowing of the heart rate produced by methoxamine could be elicited repeatedly in the same animal. Methoxamine was injected at A, B and C and caused rises in blood pressure of 50, 45 and 55 mm Hg for durations of 28, 30 and 35 min respectively. Lower record: (*a*) control response to methoxamine on the heart rate, blood pressure rose 65 mm Hg for 22 min; (*b*) heart rate response to the same dose of methoxamine after injecting phenoxybenzamine (10 mg/kg) before zero time, with no pressor effect; (*c*) methoxamine (at arrow) after phenoxybenzamine and cardiac sympathectomy before zero time, with no pressor effect.

injections of adrenaline (0.5 μg/kg), noradrenaline (1.0 μg/kg) and isoprenaline (0.1 μg/kg) and by cardiac sympathetic nerve stimulation was recorded before and after administration of methoxamine (0.5 and 1.0 mg/kg) in four cats in which the heart had been acutely denervated and phenoxybenzamine (10 mg/kg) had been injected (Table 2). Adrenaline, noradrenaline and isoprenaline increased the heart rate by an average of 16.0, 20.0 and 24.0% respectively. After methoxamine (0.5 mg/kg) these increases were reduced to

TABLE 2

EFFECT OF METHOXAMINE ON THE RESPONSES OF THE HEART RATE OF CATS TO SYMPATHOMIMETIC AMINES AND TO CARDIAC SYMPATHETIC NERVE STIMULATION

Results are means for four cats with acute cardiac sympathectomy and phenoxybenzamine (10 mg/kg)

	Heart rate after methoxamine dose								
	Nil			0·5 mg/kg			1·0 mg/kg		
Treatment	Control (per min)	Maximum (per min)	Change (%)	Control (per min)	Maximum (per min)	Change (%)	Control (per min)	Maximum (per min)	Change (%)
Isoprenaline (0·1 μg/kg)	185	230	24·0	180	202	12·0	180	184	2·0
Adrenaline (0·5 μg/kg)	188	218	16·0	184	204	11·0	180	186	3·0
Noradrenaline (1·0 μg/kg)	186	224	20·0	184	200	9·0	181	186	3·0
Sympathetic nerve stimulation	175	209	19·0	—	—	—	174	174	0·0

11.0, 9.0 and 12.0% respectively, and after methoxamine (1 mg/kg) the increases were reduced further to 3.0, 3.0 and 2.0% respectively: Table 2 also shows that the increase in heart rate of 19.0% produced by stimulation of cardiac sympathetic nerves was abolished by methoxamine (1 mg/kg).

Effect of methoxamine on the increase in rate and amplitude produced by adrenaline, noradrenaline and isoprenaline in the rat perfused heart and rabbit isolated atrial preparations. In six experiments on the perfused rat heart methoxamine (2 to 4 μg/ml.) almost abolished the increase in rate and the increase in amplitude produced by adrenaline (0.1 μg), noradrenaline (0.1 μg) and isoprenaline (0.025 μg) (Fig. 2,*a*). Similar results were obtained in four experiments on rabbit isolated atrial preparations (Fig. 2,*b*). In all these experiments methoxamine in concentrations up to 10 μg/ml. did not affect the rate or amplitude. The blocking action of methoxamine was reversible and appeared to be competitive; thus after complete blockade of the actions of the three sympathomimetic amines a tenfold increase in the dose of the amines partially overcame the blockade (Fig. 3). The specificity of blockade for sympathomimetic amines is demonstrated by the fact that responses to calcium chloride (0.2 mg/ml.) and ouabain (0.5 μg/ml.) on the atrial preparations were not depressed by methoxamine (Fig. 3).

Effects of methoxamine on the response of the cat blood pressure to adrenaline, noradrenaline and isoprenaline. In two experiments adrenaline (0.1 μg/kg) and isoprenaline (0.05 μg/kg) produced a decrease and noradrenaline (0.5 μg/kg) an increase in arterial blood pressure. When these amines were injected after the rise in blood pressure produced by methoxamine had subsided, adrenaline produced a pressor effect and isoprenaline a reduced depressor effect. An additional dose of methoxamine (0.5 mg/kg) abolished the depressor effect of isoprenaline and enhanced the pressor effect of adrenaline. The rise in blood pressure produced by noradrenaline was not altered by either concentration of methoxamine (Fig. 4).

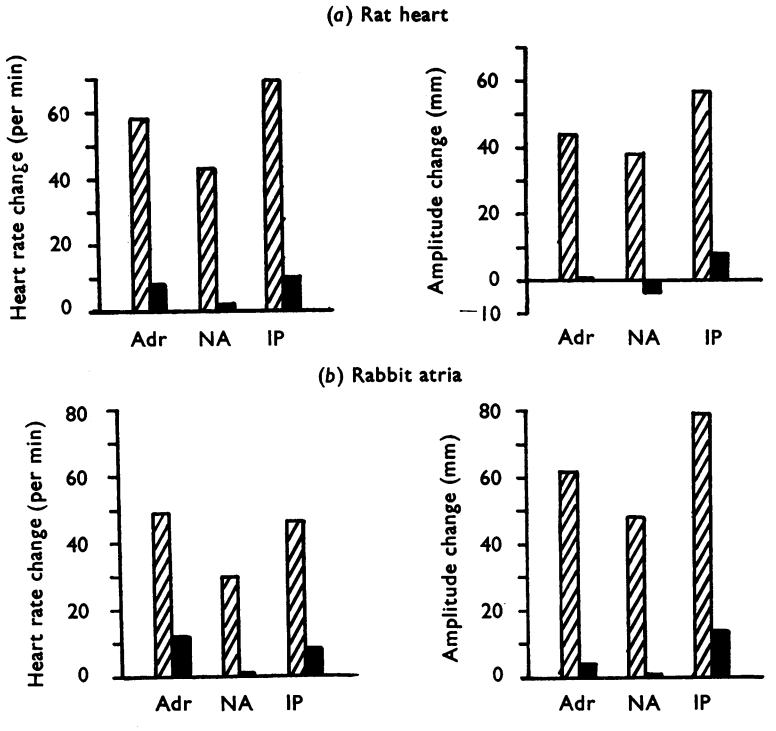

Fig. 2. Effect of methoxamine on the increase in rate and amplitude due to adrenaline (Adr), noradrenaline (NA) and isoprenaline (IP) on the rat isolated perfused heart and rabbit isolated atrial preparations. (*a*) Perfused rat hearts: hatched columns, control responses to adrenaline (0.1 μg), noradrenaline (0.1 μg) and isoprenaline (0.025 μg); filled columns, responses with 2 μg/ml. of methoxamine in the perfusion fluid. (*b*) As (*a*) but for rabbit atrial preparations and 4 μg/ml. of methoxamine; concentrations: adrenaline and noradrenaline, 0.05 μg/ml.; isoprenaline, 0.025 μg/ml.

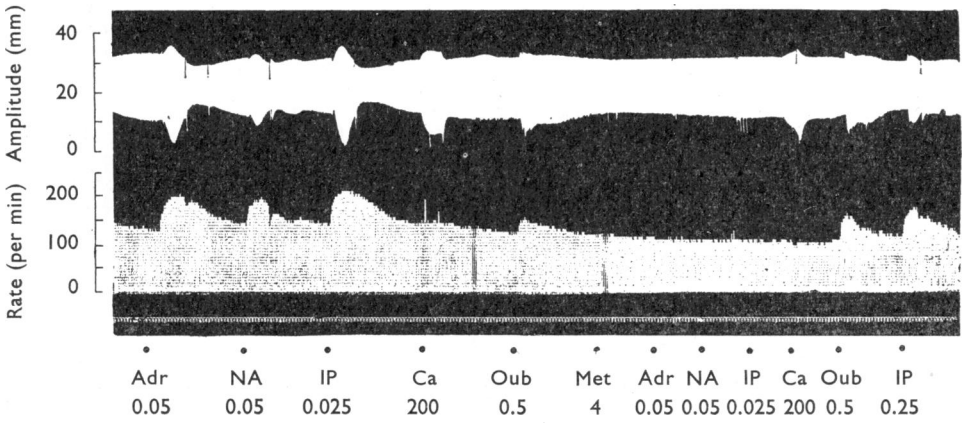

Fig. 3. Effect of methoxamine (Met) on the responses of rabbit isolated atria to adrenaline (Adr), noradrenaline (NA), isoprenaline (IP), calcium chloride (Ca) and ouabain (Oub). Upper trace, amplitude of contraction of the atria; middle trace, rate of atrial beats; lower trace, time, 30 sec. All drug concentrations in μg/ml.

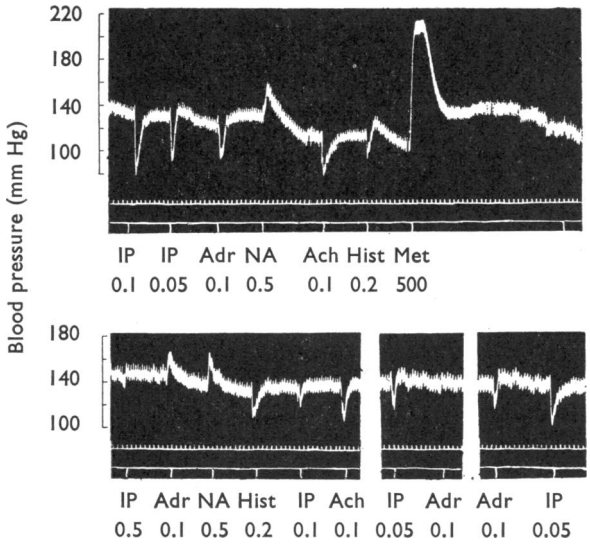

Fig. 4. Effect of methoxamine (Met) on the blood pressure responses of an anaesthetized cat (2.4 kg) to isoprenaline (IP), adrenaline (Adr), noradrenaline (NA), acetylcholine (Ach) and histamine (Hist). Time, 30 sec. All doses in μg/kg. The bottom centre and right-hand records were 75 and 135 min respectively after injection of methoxamine.

In four cats given phenoxybenzamine (5 or 10 mg/kg, 30 min beforehand) the depressor action of isoprenaline was reduced following 0.5 mg/kg of methoxamine and was abolished after an additional 0.5 mg/kg of methoxamine. The fall in blood pressure produced by adrenaline was abolished by methoxamine (0.5 mg/kg) in cats treated with phenoxybenz-

TABLE 3

EFFECTS OF METHOXAMINE ON BLOOD PRESSURE OF ANAESTHETIZED CATS

Values are means for two cats anaesthetized with chloralose for each dose of phenoxybenzamine

			Blood pressure after methoxamine dose					
			Nil		0·5 mg/kg		1·0 mg/kg	
Condition	Drug	Dose (μg/kg)	Control (mm Hg)	Change (mm Hg)	Control (mm Hg)	Change (mm Hg)	Control (mm Hg)	Change (mm Hg)
No phenoxybenzamine	Adrenaline	0·1	162·5	−41·5	163·0	+12·0	159·25	+26·50
	Noradrenaline	0·5	160·0	+38·0	161·5	+39·5	158·00	+38·5
	Isoprenaline	0·05	165·5	−48·0	168·25	−12·5	160·4	+2·5
Phenoxybenzamine (5 mg/kg)	Adrenaline	0·1	85·0	−35·5	84·5	+11·0	80·25	+18·5
	Noradrenaline	0·5	84·0	+15·25	80·0	+16·5	82·50	+14·25
	Isoprenaline	0·05	85·5	−44·0	81·5	−14·5	83·25	−1·5
Phenoxybenzamine (10 mg/kg)	Adrenaline	0·1	70·5	−30·0	75·5	−6·5	72·25	0
	Noradrenaline	0·5	72·0	0	72·0	0	71·5	0
	Isoprenaline	0·05	71·0	−32·0	71·5	−4·5	70·0	0
	Acetylcholine	0·1	70·0	−28·5	70·0	−26·0	72·0	−27·5
	Histamine	0·2	71·0	−25·0	70·0	−25·0	71·5	−24·0

amine (10 mg/kg) and was converted into a small rise in animals injected with 5 mg/kg of phenoxybenzamine. In two cats treated with 5 mg/kg of phenoxybenzamine, noradrenaline produced a small pressor response, which was not changed even by a large dose of methoxamine (5 mg/kg) (Table 3).

The selective antagonism of the vasodepressor actions of adrenaline and isoprenaline is clearly demonstrated by the fact that the fall of blood pressure produced by either acetylcholine or histamine was not reduced by methoxamine (1 mg/kg) (Table 3; Fig. 4). In the two cats treated with phenoxybenzamine (10 mg/kg) the duration of action of methoxamine (1 mg/kg) in antagonizing the vasodepressor actions of adrenaline and isoprenaline was between 140 and 185 min.

Effect of methoxamine on the inhibitory actions of adrenaline and isoprenaline on the movement of cat uterus in situ. In three of the above experiments uterine movements were also recorded. The inhibition of these movements by adrenaline (0.1 μg/kg) and isoprenaline (0.05 μg/kg) were prevented by methoxamine (0.5 mg/kg). Injected alone, however, methoxamine had no effect on the uterine movements (Fig. 5).

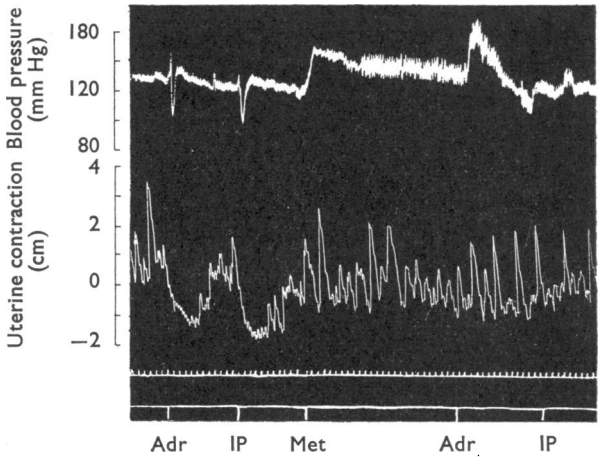

Fig. 5. Effect of methoxamine (Met, 0.5 mg/kg) on the blood pressure responses (upper trace) and uterine contraction (lower trace) of a cat (3.1 kg) to adrenaline (Adr, 0.1 μg/kg) and isoprenaline (IP, 0.05 μg/kg). Time, 30 sec.

Experiments with rabbit isolated ileum preparation. In the experiments on rabbit ileum, methoxamine (0.1 to 0.5 μg/ml.) blocked only partially the relaxations produced by adrenaline, noradrenaline and isoprenaline. In some experiments in which the inhibitory actions of the three sympathomimetic amines were recorded after addition of phentolamine (1 μg/ml.) in the Tyrode solution, methoxamine (0.1 to 0.5 μg/ml.) blocked the effects of all three amines.

DISCUSSION

The advantages attributed to the clinical use of methoxamine are that it has neither a cardioaccelerator action nor does it cause ventricular arrhythmia during anaesthesia (Hjort *et al.*, 1948). According to Welch, Braunwald, Case & Sarnoff (1958) the pressor effect of this drug is solely due to its powerful vasoconstrictor action. However, methoxamine has been said to slow the heart (Hjort *et al.*, 1948; Stutzman *et al.*, 1949; Laht

et al., 1955), protect against the cardiac arrhythmic action of adrenaline (Lahti *et al.*, 1955) and reverse the vasodepressor action of adrenaline (Levy & Ahlquist, 1957). From the results presented here these latter actions of methoxamine can be explained in terms of block of the sympathetic β-receptors. According to Aviado & Wnuck (1957) the slowing of the heart rate by methoxamine in dogs is due to hypertensive stimulation of the carotid sinus and aortic arch baroreceptors. In the cat, however, these baroreceptors do not appear to play a major role in producing bradycardia, since methoxamine reduces the heart rate after denervation of the carotid sinus and the aortic arch. After cardiac sympathectomy or after depletion of catechol amines by reserpine, methoxamine does not alter the heart rate significantly, which suggests that methoxamine acts by inhibiting the action of noradrenaline liberated at the cardiac sympathetic nerve endings. This view was substantiated in the experiments which showed that methoxamine antagonizes the increase in rate and amplitude produced by adrenaline, noradrenaline and isoprenaline on the cat heart *in situ* and on the rat isolated heart and rabbit isolated atria.

According to Lahti *et al.* (1955) methoxamine protects the ventricles from arrhythmia produced by combinations of adrenaline and cyclopropane and of adrenaline and chloroform. Similar inhibition of cardiac arrhythmia produced by adrenaline and noradrenaline in the dog has been observed with another sympathetic β-receptor blocking agent—dichloroisoprenaline (Moran & Perkins, 1958).

Levy & Ahlquist (1957) consider that the mechanisms by which ephedrine and methoxamine reverse the depressor action of adrenaline are similar. They have rejected the idea that methoxamine inhibits the vasodilator action of catechol amines in view of their finding that the depressor action of isoprenaline is only briefly diminished after ephedrine. Their conclusion that the reversal of the vasodepressor action of adrenaline in cats treated with phenoxybenzamine (3 mg/kg) is due to the " displacement " of phenoxybenzamine by methoxamine is now difficult to maintain. Even in animals not treated with phenoxybenzamine, methoxamine (0.5 to 1 mg/kg) reverses the depressor action of adrenaline and the vasodepression produced by isoprenaline is abolished. In cats treated with phenoxybenzamine, methoxamine (0.5 to 1 mg/kg) reverses the vasodepressor action of adrenaline only when the concentration of the sympatholytic drug is insufficient to produce complete α-receptor block. When blocking with phenoxybenzamine (10 mg/kg) is complete (as indicated by the abolition of the vasopressor action of noradrenaline) even a large dose of methoxamine (5 mg/kg) abolishes the depressor action of adrenaline and isoprenaline without reversing the former. Powell & Slater (1958) have reported the reversal of the vasodepressor action of adrenaline by dichloroisoprenaline in cats previously injected with dibenamine (10 mg/kg) and this was attributed by them to incomplete α-receptor block. From the results presented here the more consistent explanation for the action of methoxamine appears to be the blocking of the β-receptors.

This conclusion is also supported by the results of experiments on cat uterus and rabbit ileum preparations. According to Ahlquist (1948, 1962) the uterus contains only β-receptors whereas the intestine has α- and β-receptors and both respond by producing relaxation of the intestine. The inhibition of the movements of uterus in the cat by adrenaline and isoprenaline is completely abolished by methoxamine. Only in the presence of phentolamine, a drug known to block inhibitory α-receptors of the intestine, does methoxamine antagonize completely the inhibitory actions of adrenaline, noradrenaline and isoprenaline.

SUMMARY

1. In anaesthetized cats the pressor action of methoxamine is accompanied by a slowing of the heart. Denervation of the carotid sinuses and the aortic arch, or abolition of the pressor action of methoxamine by a previous injection of phenoxybenzamine, reduces the intensity of the bradycardia due to methoxamine.

2. This residual bradycardia was absent in cats either after cardiac sympathetic denervation or after treatment with reserpine.

3. Methoxamine also antagonizes the cardiac stimulant actions of adrenaline, noradrenaline and isoprenaline in the cat, in the rat perfused heart and in the rabbit isolated atrial preparations.

4. Methoxamine also abolishes the vasodepressor effect and inhibition of uterine movement in cats produced by adrenaline and isoprenaline and reduces the inhibition of pendulum movement of rabbit ileum produced by adrenaline, noradrenaline and isoprenaline.

5. It is concluded that methoxamine acts as an antagonist of β-receptors for catechol amines.

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