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RESPONSES OF THE CARDIOVASCULAR SYSTEM OF THE RAT TO NORADRENALINE INFUSIONS AND THEIR MODIFICATION BY ADRENOCEPTOR BLOCKING AGENTS

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1 The effects of noradrenaline upon the cardiovascular system of the rat, anaesthetized with pentobarbitone, have been investigated.

2 Noradrenaline produces a dose-dependent increase in mean arterial blood pressure (MABP) which is due entirely to an increase in cardiac output; total peripheral vascular resistance (TPR) remains unchanged.

3 Following β-adrenoceptor blockade the pressor response to infused noradrenaline is enhanced and is now due mainly to an increase in TPR; the increment in cardiac output is reduced.

4 After α-adrenoceptor blockade the pressor response is greatly reduced; the residual increase in MABP is due solely to an increase in cardiac output.

5 After ganglion blockade resting cardiac output and TPR both fall, resulting in a reduction in MABP. The pressor response to noradrenaline is enhanced and is now due to increases in both TPR and in cardiac output.

6 The cardiovascular response of the anaesthetized rat to noradrenaline can be explained in terms of classical α- and β-adrenoceptor stimulation by the amine; the unusual form of the response may be due to an effective predominance of β-adrenoceptor-mediated effects in this species.

7 It is suggested that the failure of exogenous noradrenaline to produce a rise in TPR results from a balance between the α-adrenoceptor-mediated increase and β-adrenoceptor-mediated decrease in this variable. However, this proposed balance is lost if resting vasoconstrictor tone is reduced by ganglion blockade.

Introduction

Although it is generally recognized that intravenous administration of noradrenaline raises the arterial blood pressure in mammals, the mechanism whereby this is achieved appears to vary with the species. In man, the increase in arterial blood pressure is brought about by an increase in total peripheral vascular resistance (TPR) despite a concomitant fall in cardiac output (Barcroft & Starr, 1951; Eckstein & Abboud, 1962). Similar changes occur in the cat (Greenway & Lawson, 1966). In the dog, Levy & Brind (1957) and Shanks (1966) found that the pressor effect of noradrenaline is brought about by an increase in both TPR and in cardiac output, whereas Eckstein, Abboud & Pereda (1962) described an increase in TPR with little alteration in cardiac output. These findings suggest that the primary determinant of the pressor response to noradrenaline in these three species is an increased TPR; the changes in cardiac output being small.

In the light of these results the cardiovascular responses of the rat appear to be unusual since a change in cardiac output is the primary determinant of the pressor response to noradrenaline, the TPR being unaffected (Imms & Neame, 1974).

The present experiments were performed to elucidate the differences observed in the rat by examining the cardiovascular responses to noradrenaline after the administration of adrenoceptor and ganglionic blocking agents.

Some preliminary results have been presented to the Physiological Society (Imms, Neame & Powis, 1974).

Methods

Thirty male rats of an SPF Wistar derived strain and of body weight between 420 and 650 g were anaesthetized with pentobarbitone sodium ('Sagatal', May & Baker, 70 mg/kg, i.p.). Supplementary doses of the anaesthetic were given as required.

The animals were further prepared for the experiment as described in the previous paper (Imms, Neame & Powis, 1977). Heart rate and arterial blood pressure were measured and cardiac output estimated by the thermal dilution method. Total peripheral vascular resistance and stroke volume were calculated from the measured variables.

Infusion of noradrenaline

Solutions of noradrenaline ((−)-noradrenaline bitartrate; 'Levophed', Winthrop) were infused through a nylon catheter inserted into the left femoral vein with a roller pump (Type MHRE7; Watson-Marlow Ltd., Falmouth, Cornwall) at flow rates between 0.12–0.15 ml/minute. The mean amounts of the catecholamine administered at each dose level were 310 ± 33 ng/min and 1480 ± 161 ng/min (mean ± s.d.).

Experimental procedure

A standard protocol was adopted for all experiments. On completion of surgery, heparin (500 i.u./kg body weight, i.v.) was given and the animals were allowed to stabilize for 5 minutes.

Six control cardiac output determinations were made after which an infusion of noradrenaline at the lower rate was started. After 5 min when arterial blood pressure and heart rate were steady, six further cardiac output estimations were made. The higher dose of noradrenaline was then infused and a further series of six thermodilution curves were obtained when a steady state had been established. Noradrenaline infusion was then stopped and after 5 min, or when MABP and heart rate had returned to resting levels, six control cardiac output determinations were made.

Following this control period, either adrenoceptor or ganglionic blockade was induced. In one group of rats ($n=7$) propranolol hydrochloride (Inderal, ICI; 1 mg/kg, i.v.) was given to produce β-adrenoceptor blockade; phentolamine mesylate (Rogitine, Ciba; 2 mg/kg, i.v.) was administered to the second group of animals ($n=7$) to produce α-adrenoceptor blockade; ganglionic blockade was produced in the third group ($n=9$) with hexamethonium (hexamethonium bromide, Sigma; 5 mg/kg, i.v. injected over 3 min) while in the fourth group of animals ($n=7$) a similar volume of 153 mM NaCl solution (1 ml/kg, i.v.) was given in place of the above drugs.

After a further 5 min for stabilization the four part schema described above was repeated. The hexamethonium-treated animals were subsequently given propranolol (1 mg/kg, i.v.) and the four part schema was again repeated.

Calculations

A mean value for cardiac output during each stage of the experimental procedure was calculated from each series of six thermodilution curves and expressed in ml/minute. Over the weight range of the 30 animals used there was no relationship between resting cardiac output and mean body weight (cardiac output = 0.042 body wt. + 64.7, $r=0.114$; $P>0.05$).

Total peripheral vascular resistance was calculated as:

$$\frac{\text{MABP (mmHg)}}{\text{Cardiac output (ml/min)}} \times 10^3$$

and expressed in mmHg ml^{-1} $min^{-1} \cdot 10^3$ (PRU). Stroke volume was calculated as the dividend of cardiac output and heart rate and expressed in ml/beat.

Responses to noradrenaline

Absolute values for the measured or derived cardiovascular variables under control conditions are given in Table 1. The cardiovascular responses obtained in each animal with noradrenaline were calculated in terms of increments or decrements from control values, and the mean responses of the animals comprising each group were expressed as mean change ± s.e. mean. The control values from which the changes in recorded or derived cardiovascular variables were calculated were obtained by interpolation between pre-infusion and post-infusion controls.

Statistical analysis

A paired t test was used to evaluate the significance of the cardiovascular responses obtained with noradrenaline before adrenoceptor or ganglionic blockade (Table 1); an unpaired t test was used for comparison of the response obtained after blockade with those obtained before.

Results

Control data

Before the administration of adrenoceptor or ganglionic blocking agents, the animals of all experimental groups were considered as a single population. The control cardiovascular data for these 30 animals is summarized in Table 1.

Table 1 The cardiovascular responses to noradrenaline in the untreated rat ($n=30$)

	Cardiac output (ml/min)	*MABP (mmHg)*	*TPR (PRU)*	*Heart rate (beats/min)*	*Stroke volume (ml/beat)*
Control (mean ± s.d.)	87.1 ± 19.1	121 ± 17	1475 ± 420	376 ± 33	0.235 ± 0.063
Responses to noradrenaline (mean change ± s.e. mean)					
300 ng/min	+18.7 ± 1.8****	+28 ± 2****	+25 ± 31	+12 ± 3****	+0.041 ± 0.005****
1500 ng/min	+32.2 ± 2.9****	+39 ± 2****	−12 ± 34	+79 ± 6****	+0.025 ± 0.007***
Post-infusion control (mean ± s.d.)	89.2 ± 19.4	112 ± 18	1327 ± 395	372 ± 33	0.240 ± 0.069

Statistical significance of the changes in response to noradrenaline are denoted: *** $P<0.005$; **** $P<0.001$).

Table 2 The cardiovascular responses to administration of adrenoceptor or ganglion-blocking agents

Mean change ± s.e. mean (% change from control value)	*Cardiac output (ml/min)*	*MABP (mmHg)*	*TPR (PRU)*	*Heart rate (beats/min)*	*Stroke volume (ml/beat)*
Effects of saline placebo ($n=7$)	−0.7 ± 6.8 (0.75%)	+4 ± 5 (3.5%)	+46 ± 78 (3.6%)	−3 ± 6 (0.83%)	−0.003 ± 0.017 (1.1%)
Effects of β-adrenoceptor blockade ($n=7$)	−0.8 ± 3.2 (0.93%)	−4 ± 6 (4.3%)	−28 ± 85 (2.5%)	−56 ± 6 **** (15.2%)	+0.047 ± 0.014* (19.9%)
Effects of α-adrenoceptor blockade ($n=7$)	−13.0 ± 2.2*** (16.0%)	−43 ± 6**** (40.6%)	−371 ± 91** (27.9%)	+3 ± 13 (0.79%)	−0.031 ± 0.009* (14.2%)
Effects of ganglion blockade ($n=9$)	−14.7 ± 4.5* (14.5%)	−46 ± 5**** (46.9%)	−410 ± 97*** (39.1%)	−50 ± 9**** (13.9%)	−0.003 ± 0.013 (1.1%)
Effects of β-blockade after ganglion blockade ($n=9$)	+1.2 ± 5.2 (1.3%)	+9 ± 5 (13.8%)	+69 ± 22* (9.2%)	−32 ± 7*** (9.9%)	+0.033 ± 0.020 (11.9%)

Statistical significance of the changes produced by adrenoceptor or ganglion blockade are denoted: * $P<0.05$; ** $P<0.01$; *** $P<0.005$; **** $P<0.001$.

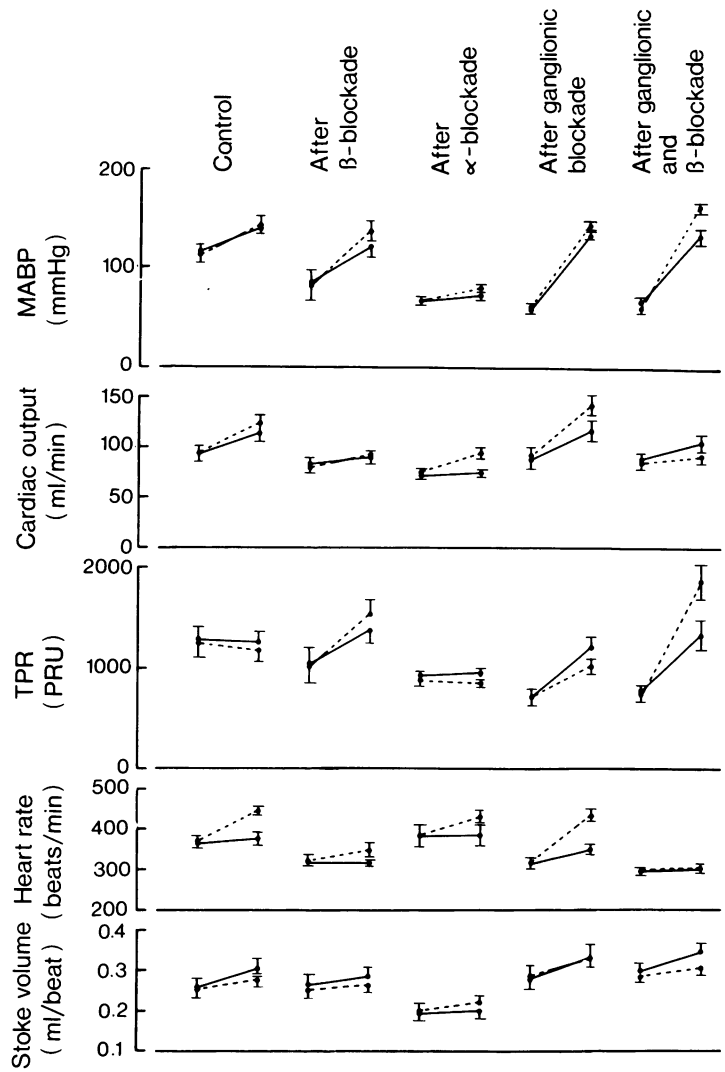

Figure 1 The effects of intravenous noradrenaline infusion at 300 ng/min (●——●) and at 1500 ng/min (●- - -●) upon total peripheral vascular resistance (TPR), cardiac output, mean arterial blood pressure (MABP), heart rate and stroke volume in control animals, and in animals in which adrenoceptor or ganglionic blockade had been produced. The left hand filled circle of each pair shows the mean resting value of each variable and the right hand filled circle shows the mean steady state value to which this is changed by noradrenaline infusion. Vertical lines indicate s.e. mean.

In these animals both doses of noradrenaline produced significant pressor responses ($P < 0.001$; Table 1). The lower rate of infusion (300 ng/min) increased the MABP by 23%; a rise that resulted from an increase in cardiac output of 21% ($P < 0.001$) with no significant change in TPR (+2%; $P > 0.5$). The increase in cardiac output was attributable largely to an increase in stroke volume of 18% ($P < 0.001$) with a small, but significant increase in heart rate ($P < 0.001$). At the higher rate of infusion (1500 ng/min) there was an increase in MABP of 32% ($P < 0.001$) which resulted from an increase in cardiac output of 36% ($P < 0.001$) with again no significant change in TPR. The increase in cardiac output was now due to an increase in heart rate of 21% ($P < 0.001$) with an increase in stroke volume of 11% ($P < 0.005$).

Administration of 153 mM NaCl solution did not cause any significant change in any of the measured cardiovascular variables (Table 2). Furthermore the cardiovascular responses to the infusions of noradrenaline were not significantly different after the saline injection from those obtained before.

The cardiovascular changes induced by noradrenaline after saline administration are shown in Figure 1 and these serve as control values with which the noradrenaline-induced cardiovascular responses obtained after adrenoceptor and ganglionic blockade can be compared.

β-Adrenoceptor blockade

Administration of propranolol did not effect MABP or cardiac output but heart rate was reduced by 56 ± 6 (mean $\pm$ s.e. mean) to 312 ± 9 beats/min ($P < 0.001$), with a compensatory increase in stroke volume (Table 2).

Following propranolol administration, the responses to infusions of noradrenaline were modified. Both doses produced greater rises in MABP than those obtained before blockade and these were now due to significant increases in TPR ($P < 0.01$) with smaller increases in cardiac output ($P < 0.05$; Figure 1).

α-Adrenoceptor blockade

Phentolamine administration was followed by an immediate fall in MABP of 41% ($P < 0.001$), which resulted from falls in both cardiac output (−16%; $P < 0.005$) and in TPR (−28%; $P < 0.01$, Table 2). The heart rate was unaffected but stroke volume was reduced by 0.031 ± 0.009 ml/beat (−14%; $P < 0.02$).

The pressor responses to infused noradrenaline were greatly reduced; the lower dose raised MABP by only 7 ± 3 mmHg ($P > 0.05$, Figure 1) and the larger dose produced an increase of 14 ± 3 mmHg ($P < 0.005$). The small change in MABP produced by the larger dose was due to an elevation of cardiac output alone, itself brought about by an increase in heart rate with a maintained stroke volume: there was no increase in TPR.

Ganglionic blockade

Hexamethonium lowered MABP by 47% ($P < 0.001$, Table 2), a fall very similar to that produced by α-adrenoceptor blockade. The fall in MABP resulted from a decrease in TPR (−39%; $P < 0.005$) and a small fall in cardiac output (−14%; $P < 0.05$). Heart rate decreased by 50 ± 9 to 310 ± 12 beats/min, a fall of similar magnitude to that obtained following β-adrenoceptor blockade.

Pressor responses to infused noradrenaline were enhanced after ganglionic blockade; the lower dose produced a rise in MABP of 76 ± 5 mmHg ($P < 0.001$), which was due to changes in both TPR (+70%; $P < 0.001$) and cardiac output (+34%; $P < 0.02$). The higher dose of noradrenaline produced a similar pressor response ($+83 \pm 5$ mmHg) as a result of an increase in TPR of 44% ($P < 0.001$) and an increase in cardiac output of 59% or 52.1 ± 7.2 ml/minute. The changes in heart rate observed after ganglionic blockade were 37 ± 6 beats/min during the lower rate infusion and 117 ± 12 beats/min during the higher rate of noradrenaline administration (Figure 1).

β-Adrenoceptor blockade after previous ganglionic blockade

Propranolol administered to the hexamethonium-treated animal had no significant effect upon MABP or cardiac output but caused a further fall in heart rate to 292 ± 7 beats min (Table 2).

The pressor response to noradrenaline infused at 300 ng/min was similar to that obtained with ganglionic blockade alone, but the increase in cardiac output was smaller and that of the TPR was larger. The higher dose of noradrenaline increased MABP by 103 ± 4 mmHg and was now due to an increase in TPR of 170% or of 1139 ± 132 PRU. Heart rate was unchanged by noradrenaline at either dose; the increase in cardiac output obtained was due to changes in stroke volume.

Discussion

Control of cardiovascular variables in the anaesthetized rat under resting conditions.

Heart rate. The resting vagal tone in the anaesthetized rat is minimal (Tipton & Taylor, 1965; De Jong & McLeod, 1967). Since there is no fall in resting heart rate following α-adrenoceptor blockade it is concluded that there is no resting drive mediated by α-adrenoceptors. β-Adrenoceptor blockade however results in a considerable fall in heart rate. This could indicate either that there is a positive chronotropic drive to the heart mediated by β-adrenoceptors or, in the light of the known membrane stabilizing effect of propranolol (Langslet, 1970; 1971), that the drug is reducing the spontaneous rate of depolarization of the pacemaker cells. Since both hexamethonium, which has no reported quinidine-like action, and depletion of catecholamines from the heart (Barrett & Carter, 1970) reduce heart rate to a similar extent as propranolol, it is suggested that there is a cardioaccelerator tone maintained by a β-adrenoceptor-mediated drive.

Vascular resistance. The presence of α- and β-adrenoceptors affecting TPR in the rat has been demonstrated previously (Debreczeni & Fenyvesi.

1971; Imms *et al.*, 1977). Furthermore the results from α-adrenoceptor blockade indicate that there is resting vasoconstrictor tone. Since ganglion blockade reduces TPR to a similar extent to α-adrenoceptor blockade, vasoconstrictor tone would appear to be mediated by autonomic nerves. The failure of propranolol to alter resting TPR implies that there is no resting β-adrenoceptor-mediated vasodilator tone.

Cardiac output. We have no direct evidence for the cause of the fall in cardiac output which follows α-adrenoceptor blockade. However, it is unlikely to be due to impairment of the heart's ability to pump blood from the veins to the arteries because phentolamine has a pronounced positive inotropic effect (Gould, Zahir & Ettinger, 1969; Das & Parratt, 1971; Nayler & Carson, 1972). The most plausible explanation therefore is that the fall results from an effect of the blocking agent on the peripheral circulation rather than upon the heart. In this connection it is possible that before blockade there was an α-adrenoceptor-mediated venoconstrictor tone. Loss of such tone would result in venous blood pooling and a reduced cardiac filling pressure with a consequent fall in cardiac output.

With regard to the effects of propranolol, we found that it slowed the heart but left the cardiac output and MABP unaltered. This means that the left ventricular stroke work must have increased solely by virtue of an increase in stroke volume. Since propranolol has a negative inotropic effect on the ventricle (Shanks, 1966) this increase in stroke work must presumably have been achieved by an increase in left heart filling pressure consequent upon β-adrenoceptor blockade.

Noradrenaline

In the cat and dog and in man, intravenous infusions of noradrenaline raise the MABP mainly by elevating the TPR (see introduction for references). However, the results presented above show clearly that in the rat, noradrenaline raises the MABP solely by increasing cardiac output. These findings are at variance with those of Takács (1964) who found that in the anaesthetized rat, as in other mammals, noradrenaline caused an elevation in MABP by raising TPR with no accompanying changes in cardiac output. This discrepancy may be one of technique for Takács determined cardiac output by a dye-dilution method requiring the removal of blood samples. In this connection a haemorrhage of as little as 1 ml per 100 g body weight of rat reduces cardiac output by 51% (Sapirstein, Sapirstein & Bredemeyer, 1960).

The results presented in the previous paper (Imms *et al.*, 1977) showed that in the anaesthetized rat the cardiovascular responses to catecholamines can be explained by their actions on α- and β-adrenoceptors as classically defined (Ahlquist, 1948), but it is possible that the unusual response of the rat to noradrenaline results from a different functional balance between these adrenoceptors compared to that observed in other animals. The resulting adrenoceptor-mediated effects may be modified however by compensatory baroreceptor reflexes, but such reflex re-adjustments appear to be weak in rats anaesthetized with pentobarbitone (De Jong & McLeod, 1967; Imms *et al.*, 1977). This conclusion is further supported by the present results: the elevation of heart rate which is observed during noradrenaline infusion is presumably the net result of direct cardiac pacemaker stimulation combined with reflex inhibitory effects induced by the rise in blood pressure. The stimulatory effects of noradrenaline are substantially reduced by β-adrenoceptor blockade but in no instance did such blockade result in a reflex fall in heart rate despite the fact that the increase in MABP with noradrenaline was as great or even greater after propranolol than before. Moreover, abolition of all neurally mediated autonomic efferent activity with hexamethonium failed to modify the absolute chronotropic increment produced by infused noradrenaline which suggests that before ganglion blockade autonomic reflex activity influencing this variable was not pronounced (see also De Jong & McLeod, 1967).

The present results give no indication of the extent of reflexly mediated falls in TPR which might result from the noradrenaline-induced rise in MABP. It would appear however that this reflex component is also minimal. Sapirstein *et al.* (1960) found that slight haemorrhage in the anaesthetized rat resulted in pronounced falls in cardiac output and in MABP which suggests that little baroreceptor mediated compensation took place. As indicated previously (Imms *et al.*, 1977) baroreceptor reflexes may be further reduced in the present experiments because the left common carotid artery is occluded for insertion of the aortic probe. It is suggested therefore that in the present experiments the observed cardiovascular effects of noradrenaline are due largely to the unmodified effects of the amine on α- and β-adrenoceptors.

Heart rate. Noradrenaline causes an increase in heart rate; this effect is mediated mainly by β-adrenoceptors since it is reduced after propranolol but is unaffected by α-adrenoceptor blockade with phentolamine.

Vascular resistance. The presence of α- and β-adrenoceptors in the rat which mediate changes in TPR has been demonstrated (Debreczeni & Takács, 1968; Debreczeni & Fenyvesi, 1971; Imms *et al.*, 1977). In addition it has been reported that there is a preponderance of β-adrenoceptors in the rat vasculature (Altura & Zweifach, 1965; Yamamoto &

Sekiya, 1969; 1972). It is possible therefore that when arterial baroreceptor reflexes are depressed, the absence of changes in TPR in the rat during noradrenaline infusion results from an equivalent degree of α-adrenoceptor-mediated vasoconstriction and β-adrenoceptor-mediated vasodilatation occurring simultaneously though not necessarily in the same vascular beds. If this degree of balanced antagonism does occur, then blockade of either type of adrenoceptor should allow the unopposed effects of the other to be observed. Blockade of β-adrenoceptors allows noradrenaline to raise TPR, presumably by its effects on α-adrenoceptors; however, blockade of α-adrenoceptors does not uncover any β-adrenoceptor-mediated fall in TPR but in these animals the prevailing vascular tone may be too low to allow further vasodilatation to occur.

An increase in TPR is obtained with noradrenaline after ganglion blockade; this increase is enhanced by subsequent β-adrenoceptor blockade which confirms the participation of these adrenoceptors in mediating noradrenaline-induced reduction in TPR. However, if our view that there is a balance between α- and β-adrenoceptors during noradrenaline infusion is correct, then it remains to be explained why large increases in TPR were obtained after ganglion blockade. It is suggested that when vasoconstrictor tone is reduced by hexamethonium an extra population of α-adrenoceptors previously engaged with endogenous noradrenaline becomes available to the infused amine. A preponderance of α-adrenoceptors available to noradrenaline thus allows the TPR to increase. Furthermore, the capacity of a vascular bed, devoid of vasoconstrictor tone, to dilate further would be reduced and any β-adrenoceptor-mediated effect must be weak. It is of interest to note that after ganglion blockade, noradrenaline infused at the lower rate raised TPR but only to a level close to the point of the proposed balance; further increase in the rate of noradrenaline infusion did not further raise TPR but in fact reduced the increment. This curtailment of the noradrenaline-induced rise in TPR is removed by subsequent β-adrenoceptor blockade which now allows a dose-dependent increase in TPR with noradrenaline (Figure 1).

Cardiac output. The action of noradrenaline in increasing cardiac output is probably both on the heart and on the peripheral circulation. The action on the heart is mediated by β-adrenoceptors since propranolol abolishes the positive chronotropic (these experiments) and inotropic responses (Shanks, 1966; Weston, 1971). However, propranolol does not abolish the increase in cardiac output obtained by infusion of noradrenaline. If it is assumed that propranolol completely blocked the cardiac actions of the infused noradrenaline, then the possibility remains that the residual increase in cardiac output is the result of a peripheral α-adrenoceptor-mediated action of the catecholamine on venules and veins. In this connection α-adrenoceptor blockade alone was found to diminish, but not abolish the noradrenaline induced increase in cardiac output.

The results of the crucial experiment of testing the effect of noradrenaline after combined α- and β-adrenoceptor blockade were equivocal because of the inability of the preparation to tolerate the combination of the blocking agents used.

Although the use of α- and β-adrenoceptor blocking agents has helped to elucidate the mechanisms of action of noradrenaline in terms of its cardiac versus peripheral actions, further studies are required to evaluate quantitatively the relative contribution of its actions on capacitance vessels to the overall response.

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