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RESPONSES OF THE CARDIOVASCULAR SYSTEM OF THE RAT TO α- AND β-ADRENOCEPTOR AGONISTS

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1 The effects of intravenously infused phenylephrine and isoprenaline upon the cardiovascular system of the rat anaesthetized with pentobarbitone, have been investigated.

2 Phenylephrine produces a dose-dependent rise in mean arterial blood pressure (MABP) that is due mainly to an increase in total peripheral vascular resistance (TPR), though at all doses tested cardiac output was invariably raised.

3 The increase in cardiac output was due in each instance to an increase in stroke volume, heart rate being unchanged. This increase in cardiac output is probably brought about by effects of phenylephrine on the capacitance vessels rather than by an effect on the heart.

4 Evidence is presented to show that the effects of phenylephrine are mediated largely by α-adrenoceptors, but that β-adrenoceptors which affect TPR are also stimulated by the amine.

5 Isoprenaline produces a dose-dependent fall in MABP that is due entirely to a fall in TPR since the cardiac output increases.

6 Unlike phenylephrine, the increase in cardiac output obtained with isoprenaline was achieved by an increase in heart rate while stroke volume remained close to control values. It is contended that the augmented venous return required for the elevated cardiac output results in this case mainly from the isoprenaline-induced fall in TPR which enhances transfer of blood from arteries to the veins.

7 Evidence is presented to show that the effects of isoprenaline are mediated mainly by β-adrenoceptors.

8 Under the present experimental conditions the adrenoceptor-mediated cardiovascular changes are little modified reflexly by the arterial baroreceptors.

Introduction

We have previously shown that the cardiovascular responses of the anaesthetized rat to noradrenaline infusion are unusual in so far as the resulting pressor response is mediated entirely by an increase in cardiac output with no alteration in total peripheral vascular resistance. That a catecholamine with predominantly α-adrenoceptor stimulating properties should raise arterial blood pressure by this means was unexpected (Imms, Neame & Powis, 1974).

It is possible that the cardiovascular system of the rat contains adrenoceptors of types different from those of other species and which respond differently to stimulation by catecholamines. It is perhaps more likely that both α- and β-adrenoceptors of the classical type are present throughout the cardiovascular system but that these have a functional balance of effects different from that which exists in other species.

To investigate these possibilities it was considered necessary to determine the cardiovascular effects of more selective α- and β-adrenoceptor agonists in this species. The present paper describes the cardiovascular effects of the α-adrenoceptor agonist phenylephrine and the β-adrenoceptor agonist isoprenaline.

Methods

Male rats of an SPF Wistar derived strain and of body weight between 420 and 600 g were anaesthetized with pentobarbitone sodium (Sagatal, May & Baker, 70 mg/kg, i.p.). Supplementary doses of the anaesthetic (6 mg, i.p.) were given as required. The trachea was cannulated and all animals breathed room air

spontaneously. Body temperature was maintained (±0.5°C) by a thermostatically controlled heated table and an overhead lamp, and was monitored from a rectal thermometer.

Measurement of arterial blood pressure

Arterial blood pressure was measured from a siliconed stainless steel cannula (i.d. 0.65 mm) containing heparinized saline (Heparin Injection B.P., Weddel Pharmaceuticals Ltd., 500 iu/ml 153 mM NaCl solution) introduced into the right femoral artery. The pressure was registered by a Bell & Howell type 4-327-L221 strain gauge transducer connected to the cannula by a short length (90 mm) of stiff nylon tubing. Mean arterial blood pressure (MABP) was extracted electronically by passing the amplified pulsatile blood pressure signal through a passive R-C network (Devices 3500) of time constant 18.5 seconds.

Measurement of heart rate

Heart rate was recorded continuously from a rate meter (Devices 3531) triggered electronically by the amplified pulsatile waveform from the arterial blood pressure transducer.

Estimation of cardiac output

Cardiac output was determined by a thermal dilution method (Fegler, 1954; Imms, Jones & Neame, 1971) in which 0.1 ml aliquots of 153 mM NaCl solution at room temperature were injected from a repeat injection apparatus (Hamilton PB600-10) into the right atrium through a catheter (o.d. 1.40 mm) advanced from the right external jugular vein. The difference in temperature between the injectate and the blood was obtained from a small thermistor of time constant approximately 100 ms (ITT U23US) mounted immediately behind the tip of the jugular venous catheter. The temperature of the aortic blood was recorded continuously from a second thermistor of similar characteristics mounted at the tip of a fine nylon tube (o.d. 0.93 mm) advanced into the aortic arch from the left common carotid artery. The thermal pulse resulting from the injection of 0.1 ml of saline at room temperature (20–24°C) into the right atrium was monitored as it passed the aortic arch thermistor.

The signal was passed through a Devices 3553 conditioning unit to a Devices 3550 d.c. chopper amplifier. The curve described was integrated with a Devices 3630 integrator and the area encompassed by the dilution curve was extracted from the integral. The integral was evaluated at the point where the recorded dilution curve, corrected for non-exponential decay, returned to the baseline. This value was incorporated into the formula given by Hanwell & Linzell (1972) to obtain a value for cardiac output in ml/minute. A more detailed description of the method used is published elsewhere (Neame, Powis & Imms, 1977).

This technique for estimating the area beneath the thermal dilution curve was compared with the methods described by Hamilton (1962) and Williams, O'Donovan & Wood (1966). All three methods were used to derive cardiac output from each of six randomly selected curves recorded during different experimental situations. The three results calculated from each curve deviated from the mean value by no more than 5%.

Recording

Arterial blood pressure, mean arterial blood pressure, heart rate, jugular and aortic temperatures and the integral of the aortic temperature change were displayed continuously on moving paper with a Devices M19 eight channel recorder.

Infusion of adrenoceptor stimulating drugs

Solutions of phenylephrine hydrochloride (Phenylephrine Injection B.P., Boots Co. Ltd.) or isoprenaline sulphate (Macarthys Ltd.) were infused through a nylon catheter inserted into the left femoral vein with a roller pump (Type MHRE7; Watson-Marlow, Falmouth, Cornwall). The concentration of the solutions used was chosen to ensure that the required amounts of the drugs (700, 1400, 2000 and 5000 ng/min phenylephrine or 20, 50, 100 and 500 ng/min isoprenaline nominal) could be infused at a flow rate between 0.10–0.15 ml/minute. The mean amounts of phenylephrine administered at each dose level in the present series of experiments were 724 ± 12 ng/min (mean ± s.d.), 1382 ± 36 ng/min, 2202 ± 123 ng/min and 4773 ± 67 ng/min while those of isoprenaline were 21.5 ± 0.6 ng/min, 49 ± 2 ng/min, 122 ± 9 ng/min and 595 ± 43 ng/minute.

Experimental procedure

The animals used constituted four experimental groups: phenylephrine was administered to one group (13 animals) at dose levels 700 and 1400 ng/min and to another group (16 animals) at 2000 and 5000 ng/minute. Into the animals of the third group (14 animals), isoprenaline was infused at 20 and 50 ng/min while into those of the fourth group (17 animals) isoprenaline was infused at 100 and 500 ng/minute.

A standard protocol was adopted for all experiments. On completion of surgery, heparin (500 iu/kg body weight) was given intravenously to all animals.

After each animal had stabilized for 5 min, six control cardiac output determinations were made after

which the infusion of either phenylephrine or isoprenaline at the lower dose was started. After 5 min when arterial blood pressure and heart rate were invariably steady, six further determinations of cardiac output were made. The higher dose of the amine was then infused and a further series of six thermodilution curves were obtained when a steady state had been established. Infusion was then stopped and after 5–10 min, or when MABP and heart rate had returned to their resting levels, six control determinations of cardiac output were made.

Following this control period, in approximately half the animals of each group the β-adrenoceptor blocking agent, propranolol hydrochloride was administered (Inderal, ICI; 1 mg/kg, i.v.), while in the remaining animals of each group a similar volume of 153 mM NaCl solution (1 ml/kg, i.v.) was given. After a further 5 min stabilization period, the four part schema described above was repeated.

Calculations

A mean value for cardiac output ±s.d. during each stage of the experimental procedure was calculated from each series of six thermodilution curves and expressed in ml/minute. The s.d. was usually about 3% of the mean value for cardiac output calculated from the six determinations; it was never greater than 7.5%. There was no significant relationship between resting cardiac output and body weight of the 60 animals used (cardiac output = 0.096 body wt + 47.1, $r=0.296$; $P\simeq 0.05$). 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} . 10^3 (PRU).

Stroke volume was calculated as the dividend of cardiac output and heart rate and expressed in ml/beat.

Expression of results

Absolute values for the measured or derived cardiovascular variables under control conditions are given in Table 1. The responses obtained with either phenylephrine or isoprenaline infusion have been expressed in two ways:

(i) In order to compare visually the overall cardiovascular response to infused phenylephrine with that produced by isoprenaline, the mean changes in each variable produced by either drug were calculated as percentage changes from the relevant control value (Figure 1).

(ii) In the written results section and in Figures 2 and 3 the cardiovascular responses obtained in each animal with either phenylephrine or isoprenaline 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 either phenylephrine or isoprenaline. The value for *t* is given by the dividend of the mean increment or decrement calculated according to (ii) above, and its s.e. mean. To compare the dose-response relationship of infused catecholamine after propranolol administration with that after saline (Figures 2 and 3) a chi-squared test was used.

Table 1 Mean control values (±s.d.) for measured and derived cardiovascular variables in 60 animals divided into four experimental groups

Group	n	*Cardiac output (ml/min)*	*Blood pressure (mmHg)*	*Heart rate (beats/min)*	*TPR (PRU)*	*Stroke volume (ml/beat)*
1. P^{700}_{1400}	13	94.1 ± 12.1	125.5 ± 12.2	397 ± 23.1	1364 ± 281	0.238 ± 0.035
2. P^{2000}_{5000}	16	96.2 ± 23.2	129.6 ± 18.1	397 ± 26.3	1434 ± 434	0.245 ± 0.068
3. I^{20}_{50}	14	96.9 ± 13.2	133.3 ± 9.4	398 ± 24.8	1399 ± 212	0.243 ± 0.028
4. I^{100}_{500}	17	93.6 ± 18.0	130.7 ± 11.2	401 ± 34.9	1441 ± 398	0.234 ± 0.043
	60	95.2 ± 17.1	129.9 ± 12.9	398 ± 27.4	1413 ± 343	0.240 ± 0.046

Under the column headed *Group,* P signifies phenylephrine infused and I signifies isoprenaline infused. The numbers following either letter denote the doses (ng/min) of each substance to be subsequently infused into the animals comprising the group.

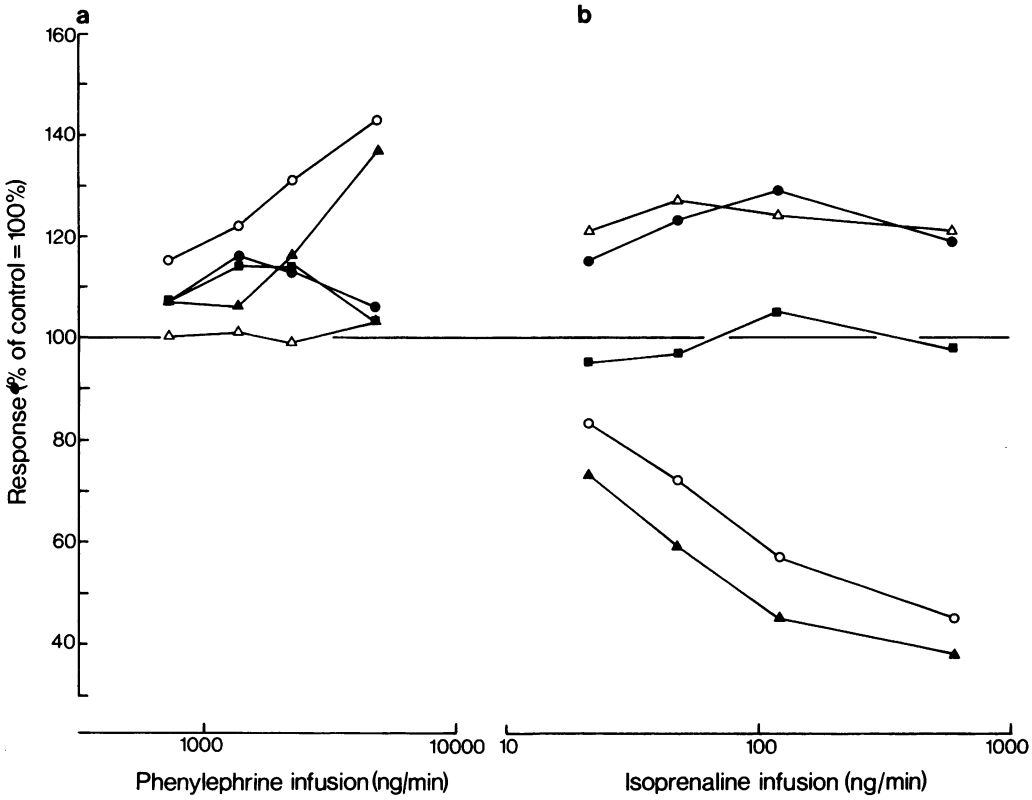

Figure 1 The cardiovascular responses of the pentobarbitone anaesthetized rat to infused (a) phenylephrine and (b) isoprenaline. The change in each measured or derived variable during infusion is expressed as a percentage of its control value. (○) Mean arterial blood pressure; (●) cardiac output; (△) heart rate; (▲) total peripheral resistance; (■) stroke volume.

Results

Control data

The mean body weight of the 60 animals used in the present series was 502 ± 53.2 g (mean $\pm$ s.d.). The mean body temperature of these animals measured after completion of surgery was 38.1 ± 0.93°C.

These 60 animals were divided into four experimental groups: the group mean values for body weight and temperature did not differ significantly from the overall mean values given above. The mean resting values for both the measured and derived cardiovascular variables in each of the four experimental groups are given in Table 1.

Effects of phenylephrine infusion

Significant pressor responses occurred at all doses infused (Figure 1a); as the rate of infusion was increased, MABP increased in a linear fashion. The increase in MABP in each case was due to increases both in TPR and in cardiac output, although at the two highest levels of infusion increases in TPR made a progressively larger contribution to the pressor response while the increase in cardiac output reached a maximum at an infusion rate of 1400 ng/min and then declined.

At the lowest rate of infusion MABP rose by 17.3 ± 2.2 mmHg (mean $\pm$ s.e. mean); an increase brought about by an increase in cardiac output of 6.9 ± 3.1 ml/min and an increase in TPR of 82 ± 36 PRU (Figure 2). At the higher rates of infusion (1400, 2000 and 5000 ng/min) MABP increased by 24.7 ± 1.5, 35.8 ± 3.9 and 48.6 ± 4.6 mmHg respectively. These rises were due to increases in TPR of 54 ± 38, 211 ± 50 and 486 ± 72 PRU and in cardiac output of 14.5 ± 3.0, 12.5 ± 2.6 and 5.5 ± 2.6 ml/minute. At no rate of infusion did the heart rate alter significantly (Figure 2).

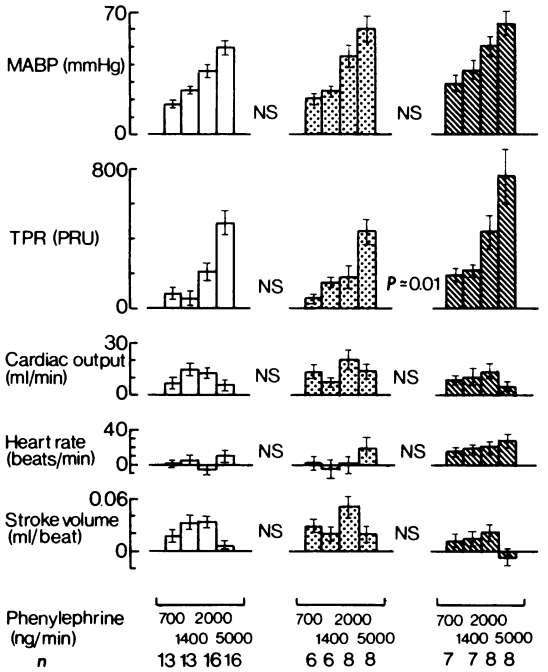

Figure 2 Mean cardiovascular changes produced by phenylephrine infused at four rates before (open columns) and after administration of either saline (dotted columns) or propranolol (hatched columns). Vertical lines show s.e. mean. The responses were compared with a chi-squared test and differences together with levels of significance are given between the groups of responses. NS signifies no difference between the groups at the 5% level of significance.

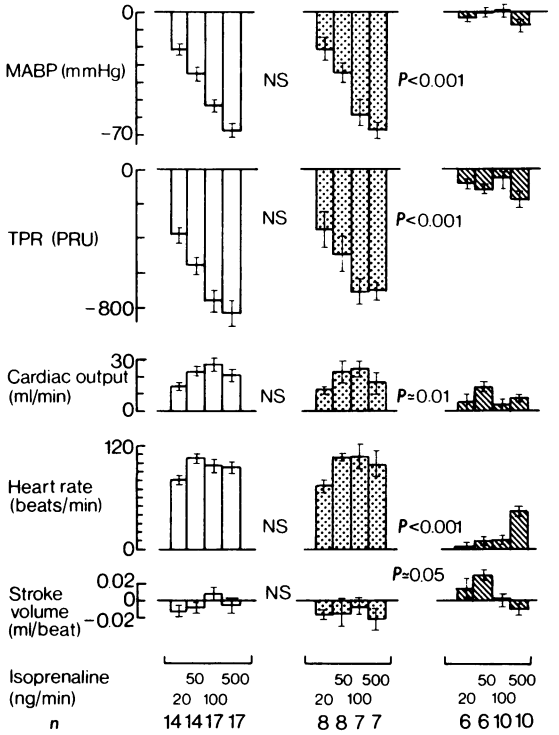

Figure 3 Mean cardiovascular changes produced by isoprenaline infused at four rates before (open columns) and after administration of either saline (dotted column) or propranolol (hatched columns). Vertical lines show s.e. mean. The responses were compared with a chi-squared test and differences together with levels of significance are given between the groups of responses. NS signifies no difference between the groups at the 5% level of significance.

Effects of isoprenaline infusion

A dose-dependent fall in MABP (Figure 1b) occurred. This was due predominantly to a decrease in TPR since at all doses cardiac output was raised. The increase in cardiac output was pronounced at the lowest rate of infusion (20 ng/min); at intermediate rates (50 and 100 ng/min) cardiac output was further increased only slightly, while at the highest infusion rate (500 ng/min), output, though significantly raised above control levels, was no greater than was obtained with the lowest rate. Figure 1b clearly shows that at all rates of isoprenaline administration stroke volume was maintained and was not significantly different from

Table 2 The cardiovascular effects of propranolol compared with those produced by saline

	n	*MABP (mmHg)*	*TPR (PRU)*	*Cardiac output (ml/min)*	*Heart rate (beats/min)*	*Stroke volume (ml/beat)*
Effects of propranolol (1 mg/kg, i.v.)	31	−12.9 ± 3.2	−50 ± 58	−5.8 ± 2.1	−62 ± 6	+0.023 ± 0.006
Effects of saline (1 ml/kg, i.v.)	29	−2.3 ± 1.5	−48 ± 23	+1.5 ± 1.4	−9 ± 3	+0.011 ± 0.003
P		<0.005	NS	<0.01	<0.001	NS

control levels ($P > 0.05$) despite a markedly increased heart rate.

At the four rates of isoprenaline infusion MABP fell by 21.3 ± 3.0, 35.3 ± 3.8, 53.9 ± 3.5 and 68.0 ± 4.1 mmHg (Figure 3). These reductions in MABP were produced by falls in TPR of 380 ± 42, 560 ± 49, 764 ± 61 and 839 ± 72 PRU respectively despite a cardiac output raised in each case by 14.0 ± 2.1, 23.0 ± 2.8, 26.9 ± 3.8 and 20.5 ± 3.2 ml/minute. At each infusion rate stroke volume was maintained at its resting level of approximately 0.238 ml/beat, while heart rate increased by 81 ± 4.7, 105 ± 4.5, 97 ± 7.4 and 95 ± 7.4 beats/min respectively.

Effects of propranolol

In 31 of the 60 animals β-adrenoceptor blockade was produced with propranolol after the second control period. In the remaining 29 animals an equivalent volume of 153 mM NaCl solution was given instead of propranolol (Table 2).

Compared with the effects of the saline, propranolol produced a significant fall in resting heart rate. This resulted in a fall in cardiac output since stroke volume was essentially unaltered by the drug. TPR was unchanged by propranolol; MABP fell slightly due to the reduced cardiac output.

Effects of phenylephrine after saline. The cardiovascular responses to the four infusion rates of phenylephrine after administration of saline were in all instances similar to, and not significantly different from the responses obtained before saline (Figure 2).

Effects of phenylephrine after propranolol. The cardiovascular responses to the four infusion rates of phenylephrine after the administration of propranolol were compared with those responses obtained after saline (Figure 2). After β-adrenoceptor blockade phenylephrine produced a significantly greater increase in TPR than before, but in all other cardiovascular variables the responses were the same.

Effects of isoprenaline after saline. The cardiovascular responses to isoprenaline infused after saline administration were in no case different from those responses obtained before saline (Figure 3).

Effects of isoprenaline after propranolol. After propranolol administration the effects of isoprenaline on the cardiovascular system were considerably altered (Figure 3). At each of the four infusion rates the induced changes in TPR and in cardiac output were significantly smaller after propranolol than after saline administration with the result that no dose of isoprenaline now caused any significant fall in MABP. It is of interest to note that after propranolol the positive chronotropic effect of isoprenaline was significantly attenuated but the changes in stroke volume were only slightly different from those obtained before.

Discussion

Infusion of phenylephrine into the pentobarbitone-anaesthetized rat produces a rise in MABP. This increase is brought about by both an increase in TPR and an increase in cardiac output; as the dose of phenylephrine increases the relative contribution of the raised TPR becomes greater. The increase in cardiac output is due entirely to an increase in stroke volume; heart rate remains virtually unchanged at any rate of infusion.

It is suggested that in this experimental preparation the modifying influences of the baroreceptors on the response to infused phenylephrine and isoprenaline are minimal and the measured responses therefore reflect the largely unmodified effects of these substances upon the heart and blood vessels of the rat. In support of this contention, since phenylephrine has been shown to have virtually no direct effect upon heart rate (Melville & Lu, 1952; Varma, Johnsen, Sherman & Youmans, 1960), it would appear that under the present experimental conditions baroreceptor-mediated changes in heart rate are minimal, otherwise a fall in this variable in response to the evoked rise in MABP would have been observed. In this connection Rothbaum, Shaw, Angell & Shock (1974) found that in the unanaesthetized rat, phenylephrine induced a considerable baroreceptor mediated fall in heart rate whereas De Jong & McLeod (1967) using anaesthetized rats found only a weak baroreceptor mediated fall in heart rate in response to a raised blood pressure produced by octapressin. Moreover a relatively small haemorrhage in the anaesthetized rat causes a marked fall in cardiac output and in MABP (Sapirstein, Sapirstein & Bredemeyer, 1960) suggesting again that the baroreceptor reflexes in anaesthetized rats are inadequate to cope even with relatively minor circulatory disturbance. In the present experiments an additional factor contributing to the loss of baroreceptor responses is that one of the vasosensory areas would have been non-functional because the aortic temperature sensing probe totally occluded the left common carotid artery.

Since the predominantly α-adrenoceptor agonist phenylephrine raises TPR, it would appear that the net vasoconstriction which this indicates is mediated by α-adrenoceptors. However, after β-adrenoceptor blockade with propranolol the increase in TPR is significantly greater, indicating a greater degree of vasoconstriction and hence that phenylephrine was previously stimulating some β-adrenoceptors which affect TPR.

The present results support the contention that the increase in cardiac output produced by infusion of phenylephrine is mediated mainly at an extracardiac location by α-adrenoceptors. Wenzel & Su (1966) found that phenylephrine exerts a negative inotropic effect on rat ventricular strips, but a number of other investigators have described weak positive inotropic effects on the rat isolated heart (see Osnes & Øye, 1975; Rothbaum *et al.*, 1974 for references) mediated by both α- and β-adrenoceptors, the latter being quantitatively more important (Weston, 1971). Any inotropic effect of the magnitude described by these authors would be unlikely to make a significant contribution to the raised cardiac output in response to phenylephrine infusion. It is probable therefore that in the absence of pronounced direct effects upon the heart, the increase in cardiac output is brought about by a Starling mechanism consequent upon a raised venous return which itself could be brought about by venoconstriction. This venoconstriction could be mediated by α-adrenoceptors since β-adrenoceptor blockade does not significantly alter the response to phenylephrine.

The limitation of the increment in cardiac output at higher rates of phenylephrine infusion could be due mainly to the rise in TPR which occurs at these levels of administration. The increased resistance to blood flow from arteries to veins which results from increasing α-adrenoceptor mediated vasoconstriction would tend to reduce venous return progressively despite any concomitant venoconstriction. In addition, the high aortic blood pressure engendered by the high TPR may itself limit the output of the heart.

Infusion of isoprenaline into the anaesthetized rat produces a fall in MABP. This is brought about entirely by a reduction in TPR, and hence by a predominance of vasodilatation, since at all levels of administration there is an increase in cardiac output. The vasodilatation is brought about mainly by the effects of isoprenaline on β-adrenoceptors since after propranolol the changes in TPR are significantly attenuated.

The increase in cardiac output which occurs during isoprenaline infusion is of interest for at each of the four infusion rates stroke volume is maintained close to its control value while heart rate is raised. The increase in heart rate is more likely to be due to direct effects of the amine upon the pacemaker than to the reduced baroreceptor activity consequent upon the fall in MABP because under our experimental conditions baroreceptor reflexes are not pronounced. Since the positive chronotropic effect is abolished by propranolol, it is mediated by β-adrenoceptors.

The evidence available does not enable us to state categorically the mechanism of the increase in cardiac output with isoprenaline. It should be noted that changes in heart rate *per se* do not necessarily influence cardiac output: if venous return remains constant, positive chronotropic responses would be compensated by inverse alterations in stroke volume. However, the reduction in stroke work (stroke volume $\times$ MABP) which we have demonstrated, combined with the positive inotropic effect that isoprenaline exerts on the rat heart (Kukovetz, Hess, Shanfeld & Haugaard, 1959; Weston, 1971) via β-adrenoceptors (Langslet, 1970; 1971) would be expected to cause a reduction in cardiac filling pressure and thereby aid the return of blood to the heart. An increase in venous return would also occur if dilatation of arteriovenous anastomoses took place. However, the most likely explanation to account for the increased cardiac output in response to isoprenaline is that the β-adrenoceptor-mediated fall in TPR induced by the amine, by reducing the resistance to blood flow from arteries to veins, enhances venous return and thus augments cardiac output. The above effects would tend to be offset by an increase in capacity of the circulation due to β-adrenoceptor mediated venodilatation which would result in pooling of blood with a consequent reduction in venous return. However, any such dilator effect which isoprenaline might have on venules and veins would appear to be relatively small because the cardiac output invariably increases in response to isoprenaline. In this connection some authors have implicated β-adrenoceptors in venoconstrictor responses in the dog (Kaiser, Ross & Braunwald, 1964) and in man (Eckstein & Hamilton, 1969). Although there is no evidence for adrenoceptors with such an action in the rat, the present results do not exclude their existence.

The cardiovascular responses obtained in the anaesthetized rat with infused phenylephrine and isoprenaline can be explained by their effects on α- and β-adrenoceptors as classically defined. The α-adrenoceptors are mainly extracardiac in location; the β-adrenoceptors are in the heart and elsewhere but probably do not cause substantial venodilatation in those capacitance vessels that regulate venous return to the heart.

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