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THE EFFECTS OF ATENOLOL ON SPONTANEOUS AND REFLEX ACTIVITY OF THE SYMPATHETIC NERVES IN THE ANAESTHETIZED CAT

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1 The reduction in the sympathetic efferent discharge observed after propranolol may be due to either a central or a peripheral effect. The β-adrenoceptor blocking drug, atenolol, is not thought to enter the brain and therefore any reduction in the level of sympathetic efferent discharge observed after atenolol is likely to be mediated peripherally rather than centrally.

2 Cats were anaesthetized with α-chloralose and artificially ventilated and a number of variables known to affect the sympathetic nerves were monitored throughout the experiment and maintained within normal limits. Recordings were made from few fibre preparations from the lumbar trunk and the renal nerves. Blood pressure was either raised or lowered by the injection of phenylephrine (1–4 μg/kg) or glyceryl trinitrate (2–20 μg/kg) and the sympathetic efferent discharge was recorded over a range of blood pressures when the blood pressure was steady.

3 Thirty min after giving atenolol (3 mg/kg) the blood pressure, heart rate and sympathetic efferent discharge were significantly reduced. Atenolol also attenuated the reflex responses of the sympathetic nerves to changes in the blood pressure.

4 It is suggested that atenolol has its actions on sympathetic nerves at a site outside the CNS and some possible mechanisms are discussed.

Introduction

β-Adrenoceptor blocking drugs are now widely used in the treatment of hypertension but their precise mechanism of action remains controversial. The reduction in cardiac output occurs acutely after β-blockade (Gibson, 1974) but the fall in blood pressure is delayed (Tarazi & Dustan, 1972) thus suggesting that the hypotensive action of these drugs cannot be solely due to a reduction in the cardiac output. Consequently, a number of different theories have been advanced to explain the hypotensive effects of the β-adrenoceptor blocking drugs. Both central and peripheral mechanisms have been suggested including actions on the release of renin and on the input from cardiovascular receptors including the baroreceptors.

There is evidence that propranolol may have central effects. Propranolol is accumulated within the brain (Myers, Lewis, Reid & Dollery, 1975) and reduces blood pressure when injected intraventricularly (e.g. Day & Roach, 1974). Intravenous infusions of propranolol have been shown to reduce the level of sympathetic efferent discharge in the conscious rabbit (Lewis & Haeusler, 1975), and these experiments have been used in support of the theory of a central action for propranolol. However the latter observations may also reflect an action on the afferent input to the brain and a subsequent modulation of the sympathetic outflow.

The present experiments were carried out to investigate the effects of the β-antagonist, atenolol, on the discharge recorded from the sympathetic efferent nerves. Atenolol has a low lipid-solubility and therefore is not likely to cross the blood-brain barrier (Barrett, 1977). Therefore any changes in the level of discharge recorded after atenolol are more likely to have been mediated by a peripheral rather than a central effect.

Methods

Experiments were carried out on 11 cats of either sex weighing between 1.78 and 2.73 kg. The animals were anaesthetized by an intraperitoneal injection of α-chloralose in polyethylene glycol (100 mg/ml) in a dose of 80 mg/kg. Further injections of α-chloralose were given intravenously in doses of 5 to 16 mg kg^{-1} h^{-1} as necessary to maintain the animals in a steady state of light anaesthesia.

The trachea was cannulated and positive pressure

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ventilation was established with a mixture of 40% O_2 in air. The femoral artery and vein were cannulated in the groin. The pH, P_{CO_2} and P_{O_2} of the arterial blood were monitored throughout the experiment. The ventilation volume was adjusted to maintain the arterial P_{CO_2} at approximately 35 mmHg and infusions of sodium bicarbonate (1 mEq/ml) were given as necessary to correct for the presence of any non-respiratory acidosis using the *in vivo* titration curves of Kappagoda, Linden & Snow (1970). Rectal temperature was monitored and maintained between 37 and 38°C. Dextraven 150 was given during the experiment to compensate for any loss of fluid. The total volume of fluid given over the period of an experiment into each animal was approximately 10–15% of its blood volume (assumed to be 80 ml/kg). Blood pressure was monitored throughout the experiment through a cannula inserted into the femoral artery and attached to a strain gauge manometer (Model P23 Gb, Statham Inst. Co. Inc. Puerto Rico). The mean pressure in the femoral artery was calculated by adding one third of the pulse pressure to the diastolic pressure.

A ventrical incision was made through the skin and abdominal muscle layers on the left side. The aorta and renal artery were exposed by a retroperitoneal approach. The skin and muscle flaps were then retracted to create an abdominal pool. Further dissection was carried out under a dissecting microscope. In one group of animals branches of the renal nerves were identified running alongside the renal artery and were dissected out from the surrounding tissue and placed on a Perspex plate. In a further group of animals, fibres were dissected from the lumbar trunk which runs alongside the aorta. The sheath and perineureum were removed, the nerve was cut and small filaments were dissected from the cut central end of the nerves and placed on platinum recording electrodes. Recordings of the discharge of these few fibre preparations from the renal nerves or the lumbar trunk were made under liquid paraffin using conventional techniques and displayed on a u.v. recorder. The mean frequency of sympathetic efferent discharge was recorded every second, either by directly counting the action potentials recorded on the u.v. paper (type 3006 S.E. Laboratories) or, in later experiments, by the use of a digital counter whose output was displayed on the u.v. paper.

Experimental protocol

Dissection of small filaments from either the renal nerves or the lumbar trunk was continued until suitable recordings from a few fibre preparation were obtained. Phenylephrine (dose 1–4 μg/kg) was then given to determine whether or not the discharge of the fibres could be altered by changes in the level of baroreceptor discharge. If the large increase in blood pressure produced by the phenylephrine did not inhibit the discharge, dissection was continued and subsequent strands tested until recordings from baroreceptor-dependent fibres were obtained.

Control records were then taken over a period of about 1 h after which the blood pressure was raised or lowered by the bolus injection of pheylephrine (1–4 μg/kg) and glyceryltrinitrate (2–20 μg/kg) respectively. Recordings of the sympathetic efferent discharge were then made over a wide range of blood pressures when the blood pressure had remained steady for at least 20 s. The blood pressure was allowed to return to control levels and further control records obtained.

Atenolol (i.v. 3 mg/kg, Tenormin, Stuart Pharmaceuticals Ltd.) was then administered. Further records were obtained at least 30 min after the administration of atenolol. The blood pressure was again raised or lowered by the use of phenylephrine or glyceryltrinitrate in the range of doses described earlier and the sympathetic efferent discharge recorded over a range of blood pressures as before.

Analysis of data

The mean blood pressure, heart rate and the level of sympathetic efferent discharge in each of the cats were compared by a non-parametric sign test and by a paired Student's *t* test.

A linear regression analysis (Snedecor & Cochran, 1967) was carried out to determine the relationship between the level of sympathetic efferent discharge and the mean blood pressure before and after giving atenolol. The differences between the slopes of the regression lines obtained before and after giving atenolol were compared for each cat, taking into account the differences in the variability of the points about the two lines. Comparisons of the slopes of the regression lines for all the cats were made using Student's paired *t* test and a non-parametric sign test.

Results

When recording started approximately 4 to 6 h after the initial dose of anaesthetic, the mean blood pressure was 122.5 mmHg (range 110–140) and the mean heart rate was 181 beats/min (range 162–204). The mean pH, P_{CO_2} and P_{O_2} of arterial blood were 7.405 (range 7.35–7.49), 39.5 mmHg (range 33.3–42.4) and 144.5 mmHg (range 91.0–200.2) respectively.

Effects of changes in blood pressure on the spontaneous discharge of few-fibre preparations from the renal nerves

The effect of changes in blood pressure on the spontaneous discharge of sympathetic efferent fibres was

investigated in 11 cats. Results from 5 animals were rejected either because of low signal to noise ratios in the recordings or if the discharge of the fibres was not influenced by changes in the blood pressure. An additional problem in these animals was that it was found impossible to maintain the animals in a steady state following the different interventions.

In 6 cats, the effect of altering the blood pressure over a range of blood pressures between 35 and 165 mmHg on the level of sympathetic efferent discharge was investigated. In each of these cats a reduction in the blood pressure resulted in an increase in the sympathetic efferent discharge whilst an increase in the blood pressure resulted in an inhibition of the discharge.

An example of the response of the renal sympathetic nerves to changes in blood pressure is shown by the open circles in Figure 1. In this cat the blood pressure was varied over the range 43 to 165 mmHg. For 10 mmHg increase in blood pressure the discharge was reduced by 0.63 impulses/s from a control value of 4.3 impulses/s recorded at a mean blood pressure of 89 mmHg. At 147 mmHg the discharge was completely inhibited.

In the 6 cats the average change in the discharge for a 10 mmHg change in the blood pressure was 2.02 ± 0.53 impulses/s (mean ± s.e. mean range 0.36–3.31 impulses/s) from a mean control value of 12.4 ± 4.4 impulses/s (range 2.6–32.7 impulses/s) recorded at a mean blood pressure of 105.5 ± 6.3 mmHg (range 87–126 mmHg). There were no detectable differences between the responses of fibres obtained from the renal nerves (cats 2, 4, 5 and 6) and the lumbar trunk (cats 1 and 3).

The changes in heart rate induced by the injection of glyceryltrinitrate and phenylephrine were highly variable. The mean increase in the heart rate produced by the injection of glyceryltrinitrate was 15 beats/min (range 4–30 beats/min) and the mean bradycardia produced by the injection of phenylephrine was 33 beats/min (range 16–54 beats/min).

Effects of atenolol

Cardiovascular effects After the administration of atenolol (3 mg/kg i.v.) there was a reduction in the mean blood pressure in each of the 6 cats. The mean blood pressure in the 6 cats during the control period was 105.5 ± 6.3 mmHg and 30 min after giving the drug it was significantly reduced to 97.6 ± 7.3 mmHg ($P < 0.01$; Student's paired t test), a mean reduction in the blood pressure of 7 mmHg (range 3–17 mmHg). This reduction resulted from significant falls in both the systolic and the diastolic blood pressures as shown in Table 1. There was also a reduction in the heart rate from 186 ± 14.5 to 150.5 ± 9.8 beats/min.

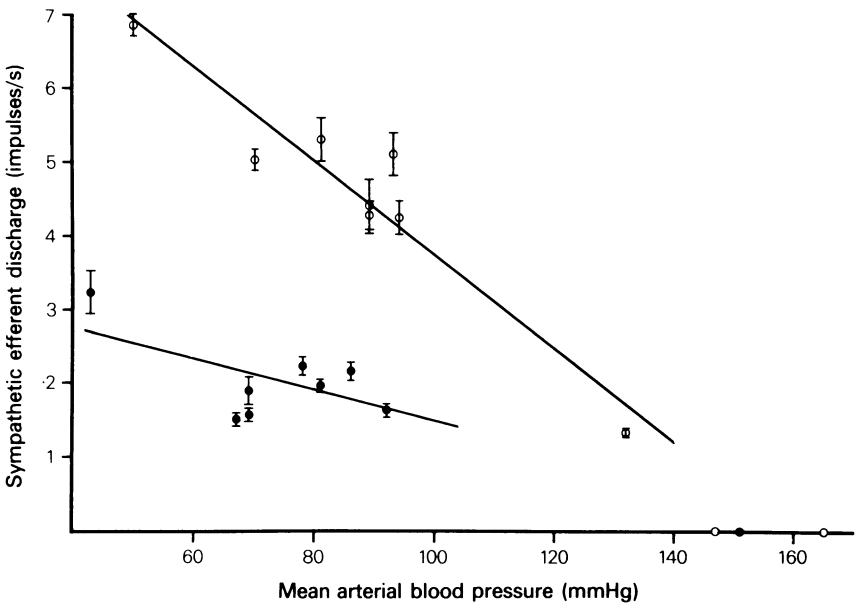

Figure 1 Effect of atenolol (3 mg/kg i.v.) on the sympathetic efferent discharge recorded from the renal nerves of a cat over a range of widely differing blood pressures: (○) measurements made before the administration of atenolol; (●) measurements made at least 30 min after the administration of atenolol. Each point shows the mean of between 4 and 12 measurements and the vertical lines represent s.e. mean.

Table 1 The effect of acute administration of atenolol (3 mg/kg) in the cat

	Before atenolol					*After administration of atenolol (3mg/kg)*				
Cat	*Fem.P. (mmHg)*			*HR*	*SED (imp/s)*	*Fem.P. (mmHg)*			*HR*	*SED (imp/s)*
No.	*Syst.*	*Diast.*	*Mean*	*(b/min)*	*(mean ± s.e. mean)*	*Syst.*	*Diast.*	*Mean*	*(b/min)*	*(mean ± s.e. mean)*
1	110	76	87	138	2.6 ± 0.2	110	66	81	138	1.5 ± 0.2
2	114	76	89	190	4.4 ± 0.3	106	64	78	147	2.2 ± 0.1
3	142	118	126	158	11.9 ± 1.0	140	114	123	120	2.4 ± 0.2
4	130	94	106	180	10.4 ± 0.6	116	76	89	140	8.3 ± 0.1
5	146	104	118	234	32.7 ± 1.1	138	98	111	174	10.5 ± 0.5
6	130	95	107	216	12.5 ± 0.8	124	94	104	184	4.4 ± 0.3
Mean ± s.e. mean	128.7	93.8	105.5	186	12.4	122.3	85.3	97.6	150.5	4.9
	5.9	6.6	6.3	14.5	4.4	5.8	8.1	7.3	9.8	1.5

From left to right: cat number; Fem.P., pressure in the femoral artery (Syst. = systolic; Diast. = diastolic and Mean pressure mmHg); HR = heart rate (beats/min) and SED = mean rate of discharge ± s.e. mean (impulses/s).

Spontaneous discharge of sympathetic efferent nerves

In each of the six cats, the administration of atenolol resulted in a reduction in the level of the discharge of sympathetic efferent nerves, in spite of the concomitant reduction in the arterial blood pressure.

Figure 2 shows original records taken from one cat before and after the administration of atenolol. In the control period the mean arterial blood pressure was 126 mmHg, the heart rate was 158 beats/min and the average rate of sympathetic efferent discharge was 11.9 impulses/s. Thirty min after atenolol there was a reduction in the heart rate to 120 beats/min and in the blood pressure to 123 mmHg and in spite of this, a large reduction in the mean level of sympathetic efferent discharge to 2.4 impulses/s.

Figure 3 illustrates the changes in the mean blood

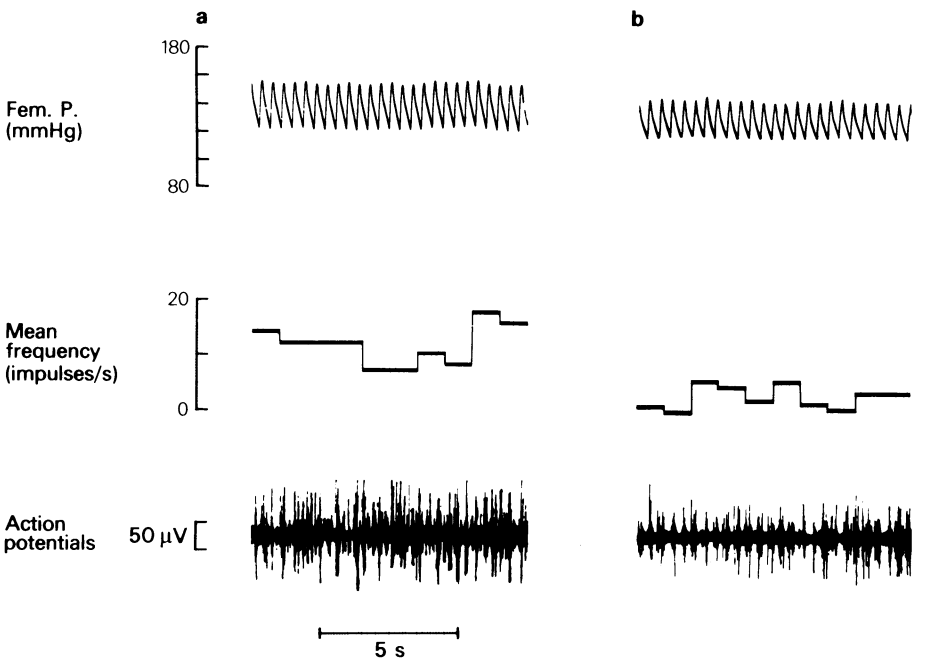

Figure 2 Original records showing the effects of the administration of atenolol: (a) before atenolol and (b) after the administration of atenolol (3 mg/kg). From above downwards: Fem.P., pressure in the femoral artery; mean frequency of sympathetic efferent discharge recorded every second; (action potentials) records of the discharge recorded from the lumbar trunk.

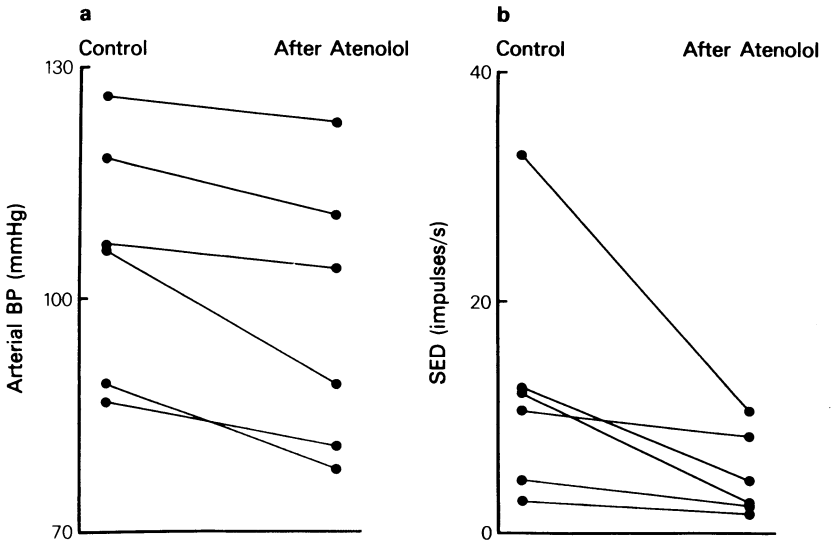

Figure 3 The effect of the administration of atenolol (3 mg/kg) on (a) the mean blood pressure and (b) sympathetic efferent discharge (SED). (a) Arterial blood pressure before and 30 min after giving atenolol in each of the 6 cats; (b) the sympathetic efferent discharge before and 30 min after giving atenolol in the same 6 cats.

pressure and sympathetic efferent discharge recorded in each of the 6 cats after giving atenolol. The mean rate of discharge before the drug was 12.4 ± 4.4 impulses/s and 30 min after atenolol this was significantly reduced to 4.9 ± 1.5 impulses/s ($P < 0.05$, $n = 6$). The mean reduction in the level of discharge was 54 ± 8.8% (range 20–80%).

Responses of the sympathetic efferent nerves to changes in blood pressure The effect of atenolol on the response of the sympathetic efferent nerves to changes in blood pressure was investigated in 6 cats. Recordings were made from the same fibres throughout each experiment. An example is shown in Figure 1. The open circles represent results obtained in the control period, as described previously and the closed circles represent results obtained after giving atenolol. For a 10 mmHg increase in blood pressure after atenolol, the discharge was reduced by 0.21 impulses/s compared to 0.63 impulses/s before giving the drug. Thus atenolol not only reduced the resting level of sympathetic efferent discharge but also attenuated the responses of the sympathetic efferent nerves to a change in the blood pressure.

In each of the 6 cats there was a significant difference in the vertical distances between the two regression lines at 60 mmHg and at 100 mmHg (P always < 0.001). The slopes of the regression lines were also compared in each of the 6 cats. In each cat the slope of the line was reduced after giving atenolol and this reduction reached a level of statistical significance ($P < 0.02$) in 5 of the 6 cats. When the results from the 6 cats are combined the results are highly significant ($P < 0.0001$).

There were no significant differences in the magnitude of the changes in blood pressure induced by injections of glyceryltrinitrate or phenylephrine after giving atenolol compared with the changes produced before giving the drug.

After atenolol, the mean increase in heart rate produced by the injection of glyceryltrinitrate was reduced to 3 beats/min but there was still a mean reduction in the heart rate of 25 beats/min as a result of the injection of phenylephrine.

Discussion

The present data provide an unequivocal demonstration of two main effects of atenolol in the anaesthetized cat: a reduction in the level of spontaneous sympathetic efferent discharge in spite of a fall in the arterial blood pressure, and an attenuation of the responses of the sympathetic efferent nerves to a pharmacologically induced change in the blood pressure.

The effect of the spontaneous discharge is in agreement with the work of Friggi, Chevalier-Cholat & Bodard (1977a) who showed a reduction in both the mean arterial blood pressure and the sympathetic efferent discharge in the anaesthetized rabbit after intravenous infusions of atenolol.

However, other workers, examining the effects of different β-antagonists on the sympathetic nerves

have obtained conflicting results. For example, Lewis & Haeusler (1975) showed a reduction both in the sympathetic efferent discharge and the blood pressure in conscious rabbits given propranolol. In the anaesthetized rabbit, sympathetic efferent discharge was reduced after the infusion of propranolol, pindolol or timolol (Friggi, Chevalier-Cholat & Torresani, 1977b). These results were not confirmed by Dorward & Korner (1978) who described a fall in the blood pressure but no change in the level of sympathetic efferent discharge in response to the intravenous infusion of propranolol. However, their findings do, in fact, suggest that there was some change in the level of sympathetic activity since it would be expected that a reduction in the blood pressure would reflexly increase the level of sympathetic efferent discharge. In the anaesthetized rabbit, infusion of acebutolol reduced both blood pressure and sympathetic activity (Chevalier-Cholat & Friggi, 1979) but in the conscious rabbit, infusion of practolol resulted in a reduction in the blood pressure but an increase in the level of sympathetic efferent discharge (Lewis, 1976). Ramage (1980) described an increase in sympathetic activity both acutely and over a period of 3 h when propranolol was given either by injection or infusion in the anaesthetized cat.

Attempts have been made by some workers (e.g. Dorward & Korner, 1978) to explain these differences. The different β-adrenoceptor blocking drugs may have different actions on the sympathetic nervous system and the actions of different drugs may vary from species to species. The presence and depth of anaesthesia may be of significance as may be the condition of the experimental animals. There is now considerable evidence that, for example, the acid-base status of the animals' blood may have profound effects on the resting discharge of the sympathetic nerves (e.g. Daly & Scott, 1962; Millar, Warden, Cooperman & Price, 1970; Preiss & Polosa, 1977) but few workers have monitored, or attempted to correct for, these changes. Thus, a deterioration in the condition of the experimental animals may modify the long-term changes in sympathetic efferent activity as a result of various drugs. Other interventions, e.g. vagotomy, may have profound effects on the sympathetic nervous discharge since vagal afferent fibres exert a tonic inhibition over the sympathetic nerves (Thorén, Donald & Shepherd, 1976) and also modify the baroreceptor reflex (Chen, Chai, Tung & Chen, 1979).

In the present experiments the condition of the animals was carefully monitored as described earlier and corrections made as necessary to maintain the animals in their original condition.

The reduction in spontaneous sympathetic efferent discharge observed by Lewis & Haeusler (1975) after infusions of propranolol has been used to provide further evidence that propranolol exerts its hypotensive effects as a result of blockade of central β-adrenoceptors. However, the changes observed might also reflect a change in the afferent input to the brain rather than solely a central effect. Atenolol is a drug with a low lipid solubility (Barrett, 1977) and therefore, unlike propranolol, is unlikely to enter the brain. Therefore the decrease in the level of sympathetic efferent discharge after the administration of atenolol, as shown by Friggi *et al.* (1977a) and by the present series of experiments, provides support for the theory that atenolol exerts its hypotensive effects by an action outside the central nervous system.

The second conclusion to be drawn from the present work is that atenolol attenuates the response of the sympathetic efferent nerves to a pharmacologically induced change in the blood pressure. A change in the sensitivity of the baroreceptor reflex arc was postulated in 1969 by Pritchard & Gillam as a possible mechanism whereby propranolol could exert its hypotensive actions. Subsequent work on this subject in both man and animals has resulted in conflicting results.

Dunlop & Shanks (1969) were able to demonstrate a reduction in the pressor response to bilateral occlusion of the common carotid arteries in anaesthetized dogs after chronic propranolol therapy although short-term administration was without effect. However, a reduction in the pressor responses to carotid occlusion and sciatic nerve stimulation was observed after a single injection of propranolol in anaesthetized cats (Korczyn & Goldberg, 1974).

Sleight and his colleagues (Smyth, Sleight & Pickering, 1969) have measured the changes in the relationship between the pulse interval and the blood pressure as a result of the injection of phenylephrine and have used the changes in this relationship as an index of changes in either the threshold or the gain of the baroreceptor reflex. Although this technique is now widely used, interpretation of their data may be questioned (see Kidd & Linden, 1975; Coote & Dodds, 1976) on the grounds, firstly that the index of baroreceptor sensitivity used by them (dependent on the linearity of the pulse interval/arterial pressure relationship over a wide range) may produce different results according to whether pressure is raised or lowered; and secondly that the experimental procedures may affect several groups of receptors each having different stimulus response relationships. The use of this index of baroreceptor function is further complicated when β-adrenoceptor blocking drugs are used since these drugs will directly alter the heart rate. Further problems arise when groups of subjects of differing ages are compared since the slope of the relationship between R-R interval and blood pressure will vary depending on the initial heart rates and blood pressures of the subjects and hence with their age (Gribbin, Pickering, Sleight & Peto, 1971). In view of the numerous problems associated with the

interpretation of data obtained by this technique it is hardly surprising that the conclusions reached have been equivocal.

The results from the present study could be explained in terms of a change in the sensitivity of the baroreceptor reflex arc. There is some evidence to support such a mechanism. Friggi *et al.* (1977b) have observed an increase in aortic baroreceptor discharge at a given blood pressure after acute administration of propranolol although a reduction in the discharge was found by Dorward & Korner (1978). After chronic treatment with propranolol, Angell-James & Bobik (1978) demonstrated a reduced threshold pressure and an increased gain of individual baroreceptor fibres in hypertensive animals.

However, a change in the baroreceptors is not the only explanation for the results obtained in the present study. Changes in the input to the brain from other receptors, for example those in the cardiopulmonary region may alter baroreceptor sensitivity as shown by Chen *et al.* 1979. Atenolol administration results in a reduction in the plasma renin activity (e.g. Wilner, Mason, Carter, Willoughby, Kochak, Cohen & Bell, 1979) and there is some evidence that changes in the renin-angiotensin system might affect the baroreceptor reflex arc (Heavey & Reid, 1978).

Finally, atenolol may also influence transmission at sympathetic ganglia. In the present series of experiments recordings were made from nerves containing both preganglionic and postganglionic fibres. Although no attempt was made to identify whether the particular fibres from which recordings were made were pre- or postganglionic, in a mixed nerve there is a tendency to record preferentially from the larger, preganglionic fibres. Therefore the results obtained in the present investigation are unlikely to be due to the effects of atenolol at sympathetic ganglia although a possible action of the drug at this site cannot be excluded.

In conclusion this work has shown two effects of atenolol; firstly, the reduction in the resting level of sympathetic efferent discharge in spite of the fall in blood pressure and secondly the attenuation of the responses of the sympathetic efferent nerves to changes in blood pressure, although the precise site of action remains speculative. These mechanisms may contribute to the hypotensive effects of the drug in the treatment of hypertension.

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