JPP Journal of Pharmacy and Pharmacology

JPP 2002, 54: 1407–1412

Received January 23, 2002
Accepted July 5, 2002
ISSN 0022-3573

Functional β_1- and β_2-adrenoceptors in the left and right atrium of pre-hypertensive rats

Sheila A. Doggrell

Abstract

There is a small increase in the functional β_2-adrenoceptor response on the spontaneously hypertensive rat (SHR) left atrium in the early stages of hypertension. In the present study, the functional β_1- and β_2-adrenoceptors of the left and right atrium in SHR pre-hypertension and age-matched (5-week-old) Wistar Kyoto (WKY) rats were characterized. Contractility methods with isoprenaline, T-0509 (a selective β_1-adrenoceptor agonist) and procaterol (a selective β_2-adrenoceptor agonist) were used. At 5 weeks, the SHRs were pre-hypertensive. Isoprenaline was more potent on the left atrium of 5-week-old SHRs than WKY rats. Bisoprolol, a selective β_1-adrenoceptor antagonist, was more potent against isoprenaline and T-0509 on the SHR than WKY rat left atrium. ICI 118,551, a selective β_2-adrenoceptor antagonist, was more potent against procaterol and T-0509 on the SHR than WKY rat left atrium. The results with bisoprolol and ICI 118,551 suggest that there are more functional β_1- and β_2-adrenoceptors on the left atrium of 5-week-old SHRs than WKY rats. Isoprenaline, T-0509 and procaterol were equipotent on the right atrium of 5-week-old WKY rats and SHRs. Bisoprolol was more potent against isoprenaline, T-0509 and procaterol on the SHR than WKY rat right atrium. ICI 118,551 was more potent against T-0509, but not isoprenaline and procaterol, on the SHR than WKY rat left atrium. This suggests there are more functional β_1-adrenoceptors, and probably more functional β_2-adrenoceptors, on the right atrium of 5-week-old SHRs than WKY rats. These functional differences in β_1- and β_2-adrenoceptor-mediated responses of the left and right atria of pre-hypertensive SHRs cannot be caused by hypertension, and may be associated with the onset of hypertension.

Cardiovascular Pharmacology Group, Faculty of Medicine and Health Sciences, The University of Auckland, Private Bag 92109, Auckland, New Zealand

Sheila A. Doggrell

Correspondence: Dr S. A. Doggrell, Department of Physiology and Pharmacology, School of Biomedical Sciences, The University of Queensland, Queensland 4072, Australia
E-mail:
s.doggrell@mailbox.uq.edu.au

Present address: Department of Physiology and Pharmacology, School of Biomedical Sciences, The University of Queensland, Queensland 4072, Australia
Sheila A. Doggrell

Funding: This research was supported by a project grant from the National Heart Foundation of New Zealand.

Introduction

In the hearts of most species, functional β_1-adrenoceptors predominate over β_2-adrenoceptors under physiological conditions (rat atria: Minneman et al 1979a, b; Juberg et al 1985; human: Brödde et al 1983; Stiles et al 1983; Buxton et al 1987). Functional responses to isoprenaline mediated by β_1-adrenoceptors decrease in the hearts of rats and humans with long-standing hypertension (Feldman 1987). There are few studies on the functional β_1- and β_2-adrenoceptors in early hypertension, and none in pre-hypertension.

The pre-hypertensive and early stages of human hypertension are characterized by a "hyperkinetic circulation" that involves an increase in cardiac output with no change in total peripheral resistance (Julius 1993). As hypertension becomes established, cardiac output returns to normal and total peripheral resistance increases (Julius 1993). Hyper-responsiveness to isoprenaline, a β-adrenoceptor stimulant, has been reported in patients with borderline hypertension and an increased cardiac output (Messerli et al 1981).

Associated with the early stages of hypertension, the spontaneously hypertensive rat (SHR) also has a hyperkinetic circulatory state (Pfeiffer & Fröhlich 1973; Smith & Hitchins 1979). In-vivo studies have shown an increased cardiac output and normal peripheral resistance in pre-hypertension, and a normal cardiac output and an increased total peripheral resistance during hypertension (Pfeiffer & Fröhlich 1973; Smith & Hitchins 1979). Thus, the SHR is a reasonable model for the onset of human hypertension.

We have previously demonstrated that there is an increase in the affinity of isoprenaline for the β_2-adrenoceptors of the SHR left atrium, which underlies the small increase in the functional β_2-adrenoceptor response during the early stages of hypertension (Doggrell & Surman 1994). It is not known whether this difference in affinity of isoprenaline for the β_2-adrenoceptors of the SHR left atria is caused by the hypertension or whether it is present pre-hypertension.

In the present study, we have characterized the functional β_1- and β_2-adrenoceptors in the left atrium in SHR pre-hypertension using the same pharmacological tools as used previously in hypertension (Doggrell & Surman 1994). The use of the same tools allowed us to compare the two studies. We have also studied the right atrium, in order to determine whether the functional β_1- and β_2-adrenoceptors are similar or different in pre-hypertension, and between the left and right atria. We determined the responses of the atria from 5-week-old WKY rats and SHRs to isoprenaline, procaterol and T-0509. Isoprenaline is a non-selective β-adrenoceptor agonist, procaterol is a selective partial agonist at β_2-adrenoceptors (O'Donnell & Wanstall 1985), and T-0509 is a selective β_1-adrenoceptor agonist (Yabana et al 1992). Subsequently, we investigated the effects of selective β_2- and β_1-adrenoceptor antagonists on the responses to isoprenaline, procaterol and T-0509. ICI 118,551 is a highly selective β_2-adrenoceptor antagonist (O'Donnell & Wanstall 1980, 1985), and bisoprolol is a highly selective β_1-adrenoceptor antagonist (Bilski et al 1983; Schliep & Harting 1984).

Materials and Methods

Drugs

The drugs used were dissolved in distilled water. They were ICI 118,551 (donated by ICI Ltd, Macclesfield, UK), atropine sulfate, guanethidine sulfate, procaterol hydrochloride and (–)-isoprenaline bitartrate (Sigma Chemicals Co., St Louis, MO, USA), and T-0509 (donated by Tanabe Seiyaku, Saitama, Japan).

Rats

Breeding pairs of WKY rats and Okamoto SHRs were purchased from the Animal Resources Centre, Perth, Western Australia, and then colonies of these rats were established in the Animal Resources Unit, School of Medicine, University of Auckland. Rats were housed three to a cage with free access to standard rat chow and water. The use of rats was approved by the University of Auckland Animal Ethics Committee in compliance with the Institutional Code of Ethical Conduct, as required by The Animals Protection Regulations 1987, which regulate the use of animals in research, testing and teaching in New Zealand.

Age and measurement of blood pressure

Five-week-old male WKY rats or SHRs were weighed and then the tail cuff blood pressure was measured using a tail plethysmograph (11TC Life Sci Model 29). The rats were matched for age: WKY rats, 36±1 days (n = 38); SHRs, 35±1 days (n = 40). The tail cuff pressures of the 5-week-old rats were not significantly different: WKY rats, 100±2 mmHg (n = 38); SHRs, 102±2 mmHg (n = 40).

Contractility experiments

Rats were stunned, exsanguinated and the heart was rapidly removed and placed in Krebs solution saturated with 5% CO_2 in oxygen. The right and left atria were dissected free. All experiments were performed in the presence of a modified Krebs solution (composition mM: NaCl, 116; KCl, 5.4; $CaCl_2$, 2.5; $MgCl_2$, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 22.0; D-glucose, 11.2) at 37°C, which was bubbled with 5% CO_2 in oxygen. Contractile responses were measured isometrically with force displacement transducers (Grass model FT03.C) and displayed on a polygraph (Grass model 79B). The rate responses of the right atrium were also subjected to a tachygraph (Grass model 7P 44B).

Separate experiments were performed with right and left atria. Left atria were mounted longitudinally between two platinum electrodes (approx. 3 cm apart, above and below the tissue). The right atrium was mounted under 0.5 g tension and left atrium under 1 g tension in 5-mL organ baths. The organ baths contained Krebs solution with guanethidine at 10^{-5} M to prevent the release of noradrenaline from sympathetic nerve endings, and atropine at 10^{-6} M to inhibit parasympathetic responses. Half of all the left atria and right atria were untreated, while the others were treated with ICI 118,551 or bisoprolol, and allowed to equilibrate for 75 min. During the equilibration period, 500 mL Krebs solution superfused the tissue. The superfusion was then stopped. Stimulation of the left atrium was at 4 Hz (duration 5 ms, 30 V) and recording of right atrium rate was commenced. After 6 min, a cumulative challenge with isoprenaline, procaterol or T-0509 was initiated with further additions on a 3-min cycle or, if a maximum response to that concentration was not obtained in 3 min, until a maximal response was obtained. The cycle was continued until an overall maximum response was obtained. Stimulation was then stopped. Untreated tissues were superfused with 500 mL β-adrenoceptor antagonist free, whereas tissues that had been treated with a β-adrenoceptor antagonist were treated with a further 500 mL over 60 min before a further challenge to isoprenaline, T-0509 or procaterol. After a third equilibration period, there was a third challenge to isoprenaline, T-0509 or procaterol. The order of challenge to isoprenaline, T-0509 or procaterol was randomized.

Data assessment

The rate increase on the right atrium and the force increase on the left atrium in the presence of isoprenaline, T-0509 or procaterol were normalized. The pD_2 (negative logarithm

of the molar concentration of agonist that causes a half maximal response) values were determined by linear regression over the straight-line part of the graph, usually 20–80% maximum response. The pK_B (negative logarithm of the molar concentration of antagonists that causes a twofold shift of the concentration response curve to the agonist) values were determined by the use of the formula: $pK_B = pK_X + \log(x-1)$, where pK_X is the negative logarithm of the molar concentration of β-blocker and x is the concentration ratio. The concentration ratio is the antilogarithm of the difference between the mean β-blocker untreated pD_2 and the individual pD_2 values in the presence of β-blocker.

Statistical analysis

Mean values ± s.e.m. were determined in all experiments. For each series of experiments, individual time control untreated tissues were run simultaneously. For each drug treatment, comparison between untreated and treated was made using Student's unpaired *t*-test. Comparison between values from WKY rats and SHRs were made using Student's unpaired *t*-test. Differences were considered significant at $P < 0.05$.

Results

Right and left atria

Responses to isoprenaline, T-0509 and procaterol

The resting rates of the right atria of 5-week-old WKY rats and SHRs were 384 ± 14 beats min^{-1} (n = 14) and 382 ± 14 beats min^{-1} (n = 16), respectively, and these values were not significantly different. Isoprenaline (10^{-10}–10^{-7} M), T-0509 (10^{-11}–10^{-5} M) and procaterol (10^{-9}–10^{-4} M) increased the rate of beating of the right atrium and the force of the electrically driven left atrium.

T-0509 was a full agonist (same sized maximum responses as isoprenaline), whereas procaterol was a partial agonist. On the 5-week-old WKY rat right atrium, the maximum response to procaterol was 59 ± 6% (n = 4) of the maximum response to isoprenaline, and similar maximums to procaterol were observed on the WKY left atrium and SHR right and left atria (data not shown).

Isoprenaline was slightly, but significantly, more potent on the left atrium of 5-week-old SHRs than WKY rats (Table 1). T-0509 and procaterol were equipotent on the WKY and SHR left atria (Table 1). Isoprenaline, T-0509 and procaterol had similar potencies on the right atrium of 5-week-old WKY rats and SHRs (Table 1). Comparison of the potencies on the left and right atria of isoprenaline, T-0509 and procaterol showed that isoprenaline and procaterol had similar potencies (Table 1). T-0509 was more potent on the left than right atria of both WKY rats and SHRs (Table 1).

Table 1 Isoprenaline, T-0509 and procaterol pD_2 values on 5-week-old Wistar Kyoto (WKY) rat and spontaneously hypertensive rat (SHR) atria.

	Left atrium	Right atrium
Isoprenaline		
WKY rat	8.96 ± 0.08 (n = 6)	8.99 ± 0.31 (n = 4)
SHR	9.29 ± 0.15 (n = 6)*	8.99 ± 0.21 (n = 5)
T-0509		
WKY rat	8.96 ± 0.12 (n = 4)	8.21 ± 0.14 (n = 4)†
SHR	8.95 ± 0.07 (n = 5)	8.58 ± 0.12 (n = 4)†
Procaterol		
WKY rat	7.44 ± 0.18 (n = 4)	7.47 ± 0.11 (n = 4)
SHR	7.67 ± 0.45 (n = 4)	7.47 ± 0.04 (n = 4)

Each value is the mean ± s.e.m. of four to six rats. *$P < 0.05$ compared with WKY rat. †$P < 0.05$ compared with WKY/SHR left atrium.

Left atrium

Effect of bisoprolol

Bisoprolol at 3×10^{-8} M caused parallel rightward shifts of the isoprenaline and procaterol responses of 5-week-old WKY and SHR left atria. Bisoprolol at 3×10^{-8} M caused non-parallel rightward shifts of the T-0509 concentration–response curves by causing a greater inhibition of the responses to low than high concentrations of T-0509. Bisoprolol at 10^{-7} M caused parallel rightward shifts of the isoprenaline and T-0509 curves.

The pK_B values for bisoprolol against isoprenaline and T-0509 were independent of the concentration of bisoprolol, and are combined in Table 2. On the WKY rat left atrium, bisoprolol was more potent against procaterol than isoprenaline ($P < 0.02$), whereas on the SHR left atrium, bisoprolol was equipotent against isoprenaline, T-0509 and procaterol (Table 2). Bisoprolol was more potent against isoprenaline and T-0509 on the SHR than WKY rat left atrium (Table 2). Bisoprolol was equipotent against procaterol on the WKY and SHR left atria (Table 2).

Effects of ICI 118,551

ICI II8,551 at 3×10^{-7} M caused parallel rightward shifts of the isoprenaline, T-0509 and procaterol concentration–responses curves of the 5-week-old WKY and SHR left atria (Figure 1). ICI 118,551 was much more potent against procaterol than isoprenaline and T-0509 on both the WKY and SHR left atria (Table 2). ICI 118,551 had a similar potency against isoprenaline on the WKY and SHR left atria (Table 2). In contrast, ICI 118,551 was more potent against procaterol and T-0509 on the SHR than WKY rat left atrium (Figure 1; Table 2).

Right atrium

Effects of bisoprolol

Bisoprolol at 3×10^{-8} M caused parallel rightward shifts of the isoprenaline, T-0509 and procaterol concentration–response curves of 5-week-old WKY and SHR right atria. On the 5-week-old SHR right atrium, bisoprolol at 10^{-7} M also caused parallel rightward shifts of the isoprenaline and T-0509 concentration–response curves. On the 5-week-old

Table 2 pK_B values for bisoprolol and ICI 118,551 against isoprenaline, procaterol and T-0509.

	Left atrium		Right atrium	
	WKY rat	SHR	WKY rat	SHR
Bisoprolol				
Isoprenaline	8.26±0.07 (n = 8)	9.16±0.01 (n = 8)*	8.03±0.22 (n = 8)	9.04±0.07 (n = 8)*
T-0509	8.54±0.05 (n = 8)	8.90±0.19 (n = 8)*	7.85±0.16 (n = 3)†	8.87±0.16 (n = 8)*
Procaterol	8.85±0.41 (n = 6)	8.87±0.25 (n = 6)	8.43±0.48 (n = 8)	9.76±0.24 (n = 8)*
ICI II8,551				
Isoprenaline	6.65±0.18 (n = 8)	6.69±0.26 (n = 8)	ND	ND
T-0509	6.80±0.24 (n = 8)	7.72±0.19 (n = 8)*	ND	7.45±0.10 (n = 8)
Procaterol	8.70±0.10 (n = 6)	9.14±0.12 (n = 5)*	9.07±0.17 (n = 6)	9.31±0.10 (n = 5)

Each value is the mean±s.e.m. of three to eight rats. *$P < 0.05$ compared with WKY rat. †$P < 0.05$ compared with WKY rat left atrium. ND, not determined.

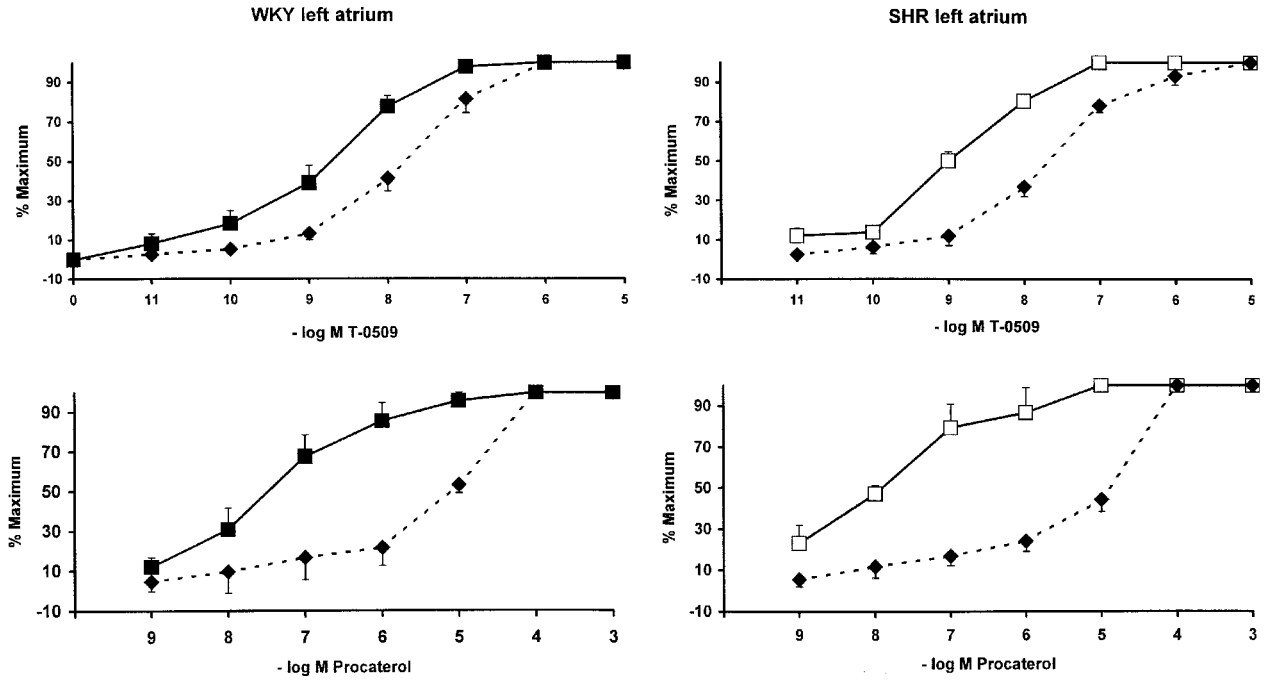

Figure 1 The effect of ICI 118,551 on responses of the left atria of 5-week-old Wistar Kyoto (WKY) rats (left panels) and spontaneously hypertensive rat (SHRs) (right panels) to T-0509 and procaterol. Responses from untreated WKY rat (■) and SHR (□) left atrium, and tissues treated with ICI 118,551 at 3×10^{-7} M (◆) were calculated as a percentage of the maximum response and plotted against the logarithm of the molar concentration of agonist. Each value is the mean±s.e.m. from four to eight left atria.

SHR right atrium, the pK_B values for bisoprolol against isoprenaline and T-0509 were independent of the concentration of bisoprolol, and are combined in Table 2. On the WKY rat right atrium, bisoprolol has a similar potency against isoprenaline, T-0509 and procaterol (Table 2). Bisoprolol was more potent against isoprenaline, procaterol and T-0509 (Figure 2) on the SHR than WKY rat right atrium (Table 2).

Effects of ICI 118,551

ICI II8,551 at 10^{-7} and 3×10^{-7} M had no effect on the isoprenaline concentration–response curves of the WKY and SHR right atria (n = 6, data not shown). ICI 118,551 at 3×10^{-7} M had no effect on the T-0509 responses of the WKY rat, but inhibited the response of SHR right atrium. ICI 118,551 at 10^{-7} M inhibited the procaterol responses of the WKY rat and SHR right atria with similar pK_B values (Table 2).

Discussion

As our colony of SHRs is pre-hypertensive at 5 weeks, the differences between SHRs and age-matched WKY rats

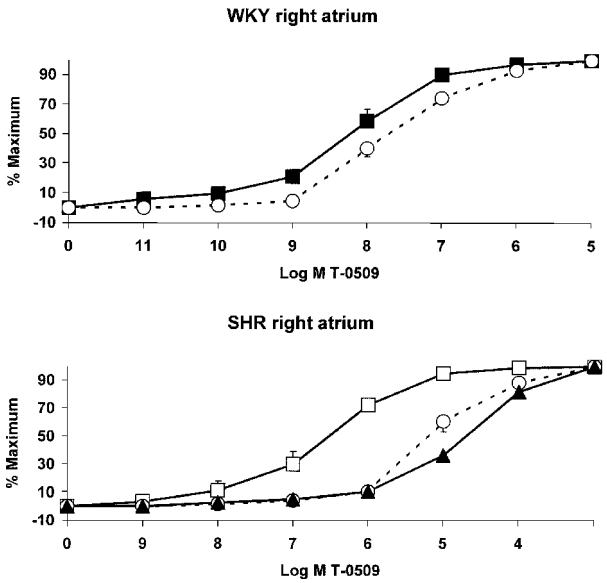

Figure 2 The effect of bisoprolol on responses of the right atria of 5-week-old Wistar Kyoto (WKY) rat and spontaneously hypertensive rat (SHR) to T-0509. Responses from untreated WKY (■) and SHR (□) left atrium, and tissues treated with bisoprolol at 3×10^{-8} (○) and 10^{-7} M (▲) were calculated as a percentage of the maximum response and plotted against the logarithm of the molar concentration of agonist. Each value is the mean±s.e.m. from four to eight left atria.

cannot be owing to hypertension. Any differences between the functional β-adrenoceptors on the atria of 5-week-old WKY and SHRs may be associated with the onset of hypertension.

One of the most interesting findings of the present study was that there was a hyper-responsiveness to isoprenaline on the left atrium, but not right atrium, of pre-hypertensive SHRs. There is no hyper-responsiveness of the left atrium to calcium chloride (Doggrell & Petcu 1997), which indicates that there is a selective hyper-responsiveness to β-adrenoceptor stimulation in pre-hypertension. There is also no left atrial hyper-responsiveness to forskolin (Doggrell & Petcu 1997), which indicates that the hyper-responsiveness to β-adrenoceptor stimulation in pre-hypertension must occur at the level of the receptor or G protein. The difference in potency for isoprenaline may reflect a greater affinity for isoprenaline at the β_1- and/or β_2-adrenoceptors of the 5-week-old SHR left atrium than the WKY rat left atrium. It is possible that the hyper-responsiveness to isoprenaline of the left atrium is associated with the increased cardiac output observed in pre-hypertension. Our finding of no hyper-responsiveness to isoprenaline on the pre-hypertensive SHR right atrium is in agreement with the findings of Dyke et al (1989).

T-0509 is considered as a selective agonist at β_1-adrenoceptors (Yabana et al 1992). In the present study, on the WKY and SHR left atria, bisoprolol at 3×10^{-8} M caused a greater inhibition of the responses to low than high concentrations of T-0509. A possible explanation for this is that low concentrations of T-0509 are stimulating predominantly left atrium β_1-adrenoceptors, whereas higher concentrations are also stimulating β_2-adrenoceptors, and this part of the response is resistant to bisoprolol.

Procaterol was initially considered highly selective for β_2-adrenoceptors (O'Donnell & Wanstall 1985). Recent evidence suggests that procaterol may stimulate β_1-adrenoceptors in addition to β_2-adrenoceptors on the left atria of 20-week-old WKY rats and SHRs. Thus, low concentrations of bisoprolol and ICI 118,551 inhibited the left atrium procaterol responses and the pK_B values for both antagonists were between their values for β_1- and β_2-adrenoceptors (Doggrell & Surman 1994). In the present study of the left and right atria of 5-week-old WKY and SHRs, low concentrations of both antagonists inhibited the procaterol responses and the pK_B values for bisoprolol and ICI 118,551 were similar to their values for β_1- and β_2-adrenoceptors, respectively. Thus, we conclude that procaterol has no selectivity for β_2- over β_1-adrenoceptors on the left and right atria of 5-week-old WKY rats and SHRs.

The present study shows that there are more functional β_1- and β_2-adrenoceptors on the left atrium of 5-week-old SHRs than WKY rats. The evidence for this is that the pK_B values for bisoprolol against T-0509 and isoprenaline were higher, and the values for ICI 118,551 against procaterol and T-0509 were also higher on the SHR than on the WKY rat. The presence of more functional β_1- and β_2-adrenoceptors on the left atrium of the pre-hypertensive SHR may be a determinant of the development of hypertension in the SHR.

At 20 weeks, there is no difference in the functional β_1-adrenoceptors of the WKY and SHR left atria (Doggrell & Surman 1994). Comparison of the data at 5 and 20 weeks shows that functional β_1-adrenoceptors remain similar on the WKY rat left atrium, as indicated by similar pK_B values for bisoprolol against isoprenaline, T-0509 and procaterol. In contrast, the lower pK_B values for bisoprolol against isoprenaline, T-0509 and procaterol on the 20-week-old compared with the 5-week-old SHR left atrium suggests that there is a loss of functional β_1-adrenoceptors between 5 and 20 weeks on the SHR left atrium.

By 20 weeks, much of the greater function of β_2-adrenoceptors that was observed on the 5-week-old SHRs, compared with age-matched WKY rat left atrium, has been lost. Comparison of the data at 5 (present study) and 20 weeks (Doggrell & Surman 1994) shows that functional β_2-adrenoceptors remain similar on the WKY rat left atrium as indicated by similar pK_B values for ICI 118,551 against isoprenaline, T-0509 and procaterol. In contrast, the lower pK_B values for ICI 118,551 against T-0509 and procaterol on the 20-week-old compared with the 5-week-old SHR left atrium suggests that there is a loss of functional β_1-adrenoceptors between 5 and 20 weeks. This study shows that the right atrium of the 5-week-old SHR may also have more functional β_1-adrenoceptors than the age-matched WKY rat. Thus, the pK_B values for bisoprolol against procaterol, isoprenaline and T-0509 were higher on the SHR than WKY rat. Unlike the left atrium, there is no clear evidence of more functional β_2-adrenoceptors in the SHR than WKY rat right atrium. The pK_B values for ICI 118,551 against procaterol were similar on the 5-week-old WKY and SHR right atria, which indicates similar

populations of functional β_2-adrenoceptors. ICI 118,551 at a concentration of 3×10^{-7} M had no effect on the T-0509 responses of the WKY, but inhibited those of the SHR, and this may indicate slightly more functional β_2-adrenoceptors in the SHR than WKY rat right atrium. ICI 118,551 at 3×10^{-7} M had no effect on the isoprenaline responses of the 5-week-old WKY and SHR right atria, which indicates that isoprenaline predominantly stimulates the β_1-adrenoceptors of the right atrium.

Procaterol has a similar potency on the left and right atria of 5-week-old WKY and SHRs. At 20 weeks, procaterol has a higher potency on the left atrium of SHRs than WKY rats (Doggrell & Surman 1994). Comparison of the pD_2 values shows that the sensitivity to procaterol decreases to a small extent on the WKY rat left atrium between 5 and 20 weeks, whereas procaterol is equipotent on the left atrium of 5- and 20-week-old SHRs. This suggests that there is a loss of functional left atrium β_2-adrenoceptors during the maturation of the WKY rat from 5 and 20 weeks, which is not observed in the SHR.

One aspect of this study was to compare the functional β_1- and β_2-adrenoceptors of the left and right atria. T-0509 was more potent on the left than right atrium. Bisoprolol was more potent against T-0509 on the left than right atrium. These findings with T-0509 suggest that there may be more functional β_1-adrenoceptors on the left than on the right atrium. An alternative explanation is that β_1-adrenoceptor excitation–contraction coupling is more efficient on the left than on the right atrium.

In conclusion, the major finding of the present study is that there are functional differences in β_1- and β_2-adrenoceptor-mediated responses of left and right atria in pre-hypertensive SHRs compared with age-matched WKY rats. The widely held view that changes in functional β_1- and β_2-adrenoceptor-mediated responses are solely owing to hypertension is no longer valid. The functional differences in β_1- and β_2-adrenoceptor-mediated responses of left and right atria in pre-hypertensive SHRs may be associated with the onset of hypertension.

References

Bilski, A. J., Halliday, S. E., Fitzgerald, J. D., Wale, J. L. (1983) The pharmacology of a β_2-selective adrenoceptor antagonist. *J. Cardiovasc. Pharmacol.* **5**: 430–437

Brödde, O.-E., Karad, K., Zerkowski, H.-R., Rohm, N., Reidemaster, J. C. (1983) Coexistence of β_1- and β_2-adrenoceptors in human right atrium. Direct identification by (±)-[^{125}I]-iodocyanopindolol binding. *Circ. Res.* **53**: 752–758

Buxton, B. F., Jones, C. R., Molenaar, P., Summers, R. J. (1987) Characterization and autoradiographic localization of β-adrenoceptor subtypes in human cardiac tissue. *Br. J. Pharmacol.* **92**: 299–310

Doggrell, S. A., Petcu, E. B. (1997) Hyper-responsiveness to isoprenaline on the atria, but not ventricles, of prehypertensive rats. *Br. J. Pharmacol.* **120**: 347

Doggrell, S. A., Surman, A. J. (1994) Functional β-adrenoceptors in the left atrium of normotensive and hypertensive rats. *J. Auton. Pharmacol.* **14**: 425–436

Dyke, A. C., Angus, J. A., Korner, P. I. (1989) A functional study of the development of the cardiac sympathetic neuroeffector junction in the SHR. *J. Hypertens.* **7**: 345–353

Feldman, R. D. (1987) β-Adrenergic receptor alterations in hypertension – physiological and molecular correlates. *Can. J. Physiol. Pharmacol.* **65**: 1666–1672

Juberg, E. N., Minneman, K. P., Abel, P. W. (1985) β_1- and β_2-adrenoceptor binding and functional response in right and left atria of rat heart. *Naunyn Schmiedebergs Arch. Pharmacol.* **330**: 193–202

Julius, S. (1993) Sympathetic hyperactivity and coronary risk in hypertension. *Hypertension* **21**: 886–893

Messerli, F. H., Kuchel, O., Hamet, P., Tolis, G., Guthrie, J., Fraysse, J., Nowaczynski, W., Genest, J. (1981) Plasma cyclic adenosine 3′5′-monophosphate response to isoproterenol and glucagon in hyperkinetic borderline (labile) hypertension. *Circ. Res.* **38** (Suppl. 2): 42–47

Minneman, K. P., Hegstrand, L. R., Molinoff, P. B. (1979a) The pharmacological specificity of beta-1 and beta-2 adrenergic receptors in the rat heart and lung *in vitro*. *Mol. Pharmacol.* **16**: 21–33

Minneman, K. P., Hegstrand, L. R., Molinoff, P. B. (1979b) Simultaneous determination of beta-1 and beta-2 adrenergic receptors in tissues containing both receptor subtypes. *Mol. Pharmacol.* **16**: 34–46

O'Donnell, S. R., Wanstall, J. C. (1980) Evidence that ICI 115,881 is a potent, highly beta$_2$-selective adrenoceptor antagonist and can be used to characterize beta-adrenoceptor populations in tissues. *Life Sci.* **27**: 671–677

O'Donnell, S. R., Wanstall, J. C. (1985) Responses to the β_2-selective agonist procaterol of vascular and atrial preparations with different β-adrenoceptor populations. *Br. J. Pharmacol.* **84**: 227–235

Pfeiffer, M. A., Fröhlich, E. D. (1973) Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. *Circ. Res.* **31** (Suppl. 1): 128–135

Schliep, H.-J., Harting, J. (1984) β_1-Selectivity of bisoprolol, a new β-adrenoceptor antagonist, in anesthetized dogs and guinea pigs. *J. Cardiovasc. Pharmacol.* **6**: 156–160

Smith, T. L., Hutchins, P. M. (1979) Central hemodynamics in the development stages of spontaneous hypertension in the anaesthetized rat. *Hypertension* **1**: 508–517

Stiles, G. L., Taylor, S., Lefkowitz, R. J. (1983) Human cardiac beta-adrenergic receptors: subtype heterogeneity delineated by direct radioligand binding. *Life Sci.* **33**: 467–473

Yabana, H., Watanabe, H., Narita, H., Nagao, T. (1992) Selective and full β_1-adrenoceptor agonist action of a catechol derivative of denopamine (T-0509) in the guinea-pig cardiac muscle and trachea: comparison with denopamine, xamoterol and isoprenaline. *Br. J. Pharmacol.* **106**: 335–341