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The Effects of Streptozotocin-induced Diabetes and Aldose Reductase Inhibition with Sorbinil, on Left and Right Atrial Function in the Rat

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Abstract

Diabetes mellitus is frequently associated with the complications of cardiovascular disease. Activation of the aldose reductase (or polyol) pathway has long been implicated as an underlying factor for the development of many diabetic complications and indeed, treatment with aldose reductase inhibitors has been shown to prevent or reverse many of these diabetic complications. This study examines the effects of 14-day streptozotocin-induced diabetes on α_1- and β-adrenoceptor-mediated responses in rat isolated left and right atria. The effects of treatment with the aldose reductase inhibitor (ARI) sorbinil were also studied. A positive inotropic response was observed to both isoprenaline and phenylephrine in left atria. Diabetes of 14 days duration resulted in a supersensitivity of these tissues to the β-adrenoceptor agonist in comparison with controls, while responses to the α_1-adrenoceptor agonist were unaltered. Spontaneously beating right atria from diabetic rats was found to have a depressed resting rate compared with control tissues, although positive chronotropic β-adrenoceptor-mediated responses were not affected by diabetes. Phenylephrine produced α_1-adrenoceptor-mediated chronotropic responses in right atrial tissues, and these were found to be enhanced in rats with diabetes. Treatment of diabetic rats with the ARI sorbinil was successful in preventing only one of the observed diabetes-induced changes in atrial function, namely the supersensitivity of left atria to isoprenaline. Sorbinil treatment did, however, alter responses of control left and right atria in a manner similar to diabetes.

In conclusion, streptozotocin-induced diabetes of 14 days duration was found to cause a number of alterations in the functioning of both left and right atria. ARI treatment with sorbinil failed to prevent all but one of these changes, and in addition altered responses of atria from control rats, having a similar effect to that produced by diabetes. These data suggest that sorbinil may have effects in addition to, and independent of, aldose reductase inhibition in the cardiovascular system.

Diabetes mellitus is associated with an increased susceptibility to cardiovascular disease and it has been suggested that alterations in myocardial function may contribute to the development of diabetic cardiovascular complications (Butler et al 1985). Diabetes can result in changes in the density of cardiac adrenoceptors or the sensitivity of cardiac tissues to adrenoceptor agonists but much inconsistency exists in the literature regarding these effects. The effect of diabetes on the responsiveness of atrial tissues to β-adrenoceptor agonists is variable (Durante et al 1989; Austin & Chess-Williams 1991; Dincer et al 1998) and both increases and decreases in cardiac α-adrenoceptor-mediated responsiveness have been observed (Heyliger et al 1982; Kamata et al 1997). Recently it has been suggested that although the contribution of α_1-adrenoceptors to positive inotropic responses is relatively small in comparison with β-adrenoceptors (Capogrossi et al 1991), in pathological conditions α_1-adrenoceptors may become more important (Terzic et al 1993). Indeed it has been reported that in diabetes α-adrenoceptor-mediated inotropic responses are enhanced in atrial tissues

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(Yu & McNeill 1991). However, the question of whether α_1-adrenoceptors can mediate a chronotropic response is still not resolved, with reports of a negative, positive and no chronotropic response to α_1-adrenoceptor stimulation (Dukes & Vaughan Williams 1984; Tung et al 1985; Brown & Carpentier 1988).

Activation of the polyol (or aldose reductase) pathway has long been implicated as one of the major underlying causes for the development of diabetic complications (Van Heyningen 1959). Since hyperglycaemia is known to activate the polyol pathway, resulting in sorbitol accumulation (Gabbay 1973), it is possible that diabetes-induced changes in cardiac adrenoceptors are due to increased flux through this pathway, and therefore may be prevented by treatment with an aldose reductase inhibitor (ARI) such as sorbinil. The effects of aldose reductase inhibition on the cardiovascular complications of diabetes are less well documented than for other diabetic complications, and the effect on cardiac adrenoceptor changes even less so. However, the elevation of β-adrenoceptor number and responsiveness found in left atria and papillary muscles of diabetic rats has previously been prevented by treatment with the ARI ponalrestat (Austin & Chess-Williams 1991); and Cameron et al (1989) reported that ARI treatment of diabetic rats prevented diabetes-induced slowing of contraction and relaxation of cardiac muscle.

The aims of this study were to investigate the effects of streptozotocin-induced diabetes of 14 days duration on the adrenoceptor-mediated responses of left and right atria from the rat and to determine whether an α_1-adrenoceptor-mediated chronotropic response could be observed. The study also investigates the effect of ARI treatment with sorbinil on diabetes-induced alterations.

Materials and Methods

Drugs

(−)-Phenylephrine hydrochloride, (±)-isoprenaline hydrochloride, (±)-propranolol hydrochloride, cocaine hydrochloride, corticosterone-21-acetate and streptozotocin were obtained from Sigma (Poole, UK). Sorbinil was a gift from Pfizer Inc. (Groton, USA).

Animals

Male Wistar rats (230–270 g) were used for all experiments. Diabetes was induced by a single intraperitoneal injection of streptozotocin ($65\,mg\,kg^{-1}$) dissolved in 0·01 M citrate buffer (pH 4·5). Age-matched control rats received citrate buffer alone and rats were allowed free access to normal rat chow and water. Blood glucose was measured at the time of death by use of glucose sensitive BM-glycaemie 1-44 test strips (Boehringer Mannheim) and a Glucochek S.C. glucose meter (Medistron Limited); rats with blood glucose levels greater than 15 mM were considered diabetic and used in the study. Body weight was recorded before initial injection and before death.

Rats to be pre-treated with the aldose reductase inhibitor received the initial intraperitoneal injection of streptozotocin or vehicle only and the following day the rats were administered an oral dose of sorbinil (Pfizer) ($25\,mg\,kg^{-1}$). Oral dosing via gavage was continued daily for two weeks.

Atria

Fourteen days after initial injection the rats were stunned and killed by exsanguination. Left and right atrial appendages were removed and rapidly suspended in 30-mL tissue baths containing Krebs-bicarbonate solution (composition in mM: NaCl, 118·4; KCl, 4·7; $NaHCO_3$, 25; glucose, 11·7; $MgSO_4$, 1·2; $KHPO_4$, 1·2; and $CaCl_2$, 1·9) gassed with 5% CO_2 in O_2 at 37°C. Left atria were mounted on bipolar electrodes and both left and right atria were attached to Lectromed UF1 force transducers, linked to a computerised CED (Cambridge Electronic Devices) system, using Chart software, for measurement of isometric developed tension and rate. The tissues were equilibrated under 0·8 g tension for 30 min and left atria were paced at 1 Hz (5 ms pulse width, threshold voltage + 50%) via Grass S48 stimulators.

Cumulative concentration–response curves were obtained first to isoprenaline and then, after a 45-min period of washing, to phenylephrine. All experiments were performed in the presence of 10 μM cocaine and corticosterone and phenylephrine curves were performed in the presence of 1 μM propranolol.

Data analysis

For left atria, increases in developed tension (dT), and rate of tension development and decline ($+dT/dt$ and $-dT/dt$, respectively) evoked by the agonist were plotted as a percentage of the maximum response for each concentration–response curve. Individual EC50 values (molar concentration producing half-maximal response) were determined and geometric mean EC50 values with

95% confidence limits calculated. In right atria, mean maximum rate increases to each agonist were calculated with s.e.m.

Differences in mean responses were analysed by analysis of variance and Student's modified *t*-test (Newman-Keuls). Significance levels for mean EC50 values were determined by analysis of variance, followed by Student's modified *t*-test applied to individual logarithmic values. $P < 0{\cdot}05$ was considered significant.

Results

Blood glucose and body weight changes

Injection of rats with streptozotocin resulted in the development of symptoms characteristic of diabetes (polydipsia, polyphagia and polyuria). Rats also suffered a significant weight loss over the 14-day period, relative to age-matched controls (Table 1). Blood glucose levels were also elevated relative to controls. Treatment of diabetic rats with sorbinil did not affect the elevated blood glucose levels. However, sorbinil treatment did cause an increased weight loss in diabetic rats. Control rats treated with sorbinil showed impaired weight gain. Blood glucose levels of control rats treated with sorbinil were not different from untreated controls.

Inotropic responses of isolated left atria

β-Adrenoceptor-mediated inotropic responses to isoprenaline. Resting developed tension in isolated left atria was not significantly different between control and diabetic rats and was not altered by treatment with sorbinil (Table 2). The addition of the β-adrenoceptor agonist isoprenaline caused a positive inotropic effect in these tissues. Maximum developed tension to isoprenaline was significantly reduced in diabetic left atria, while the tissues showed supersensitivity to this agonist as indicated by reduced EC50 values (Figure 1). Treatment of diabetic rats with sorbinil did not prevent the diabetes-induced reduction in maximum developed tension, the maximum remaining significantly lower than untreated controls. However, sorbinil treatment did prevent the supersensitivity to isoprenaline found in diabetic left atria, producing EC50 values not significantly different to untreated controls. Treatment of control rats with sorbinil also significantly altered responses of left atria, with maximum developed tension to isoprenaline being reduced when compared with untreated controls, although EC50 values were unaltered.

The rate of tension development ($+dT/dt$) and decline ($-dT/dt$) after addition of isoprenaline was also measured in left atria. The changes in $+dT/dt$ mirrored the changes in tension described above

Table 1. Mean blood glucose levels in diabetic rats (at the time of death) and weight change over 14 days.

	Control	Diabetic	Sorbinil-treated control	Sorbinil-treated diabetic
n	12	13	13	12
Blood glucose level (mM)	7·7 ± 0·3	> 16	7·6 ± 0·5	> 17
Weight change (g)	59·8 ± 5·4	−16·3 ± 2·8***	30·7 ± 3·6***	−35·3 ± 9·1***†

***$P < 0{\cdot}001$, compared with control. †$P < 0{\cdot}05$, compared with untreated diabetic rats. Values are mean ± s.e.m.

Table 2. Geometric mean EC50 values (with 95% confidence limits) and maximum responses (± s.e.m.) for isoprenaline on rat left atria.

	Control	Diabetic	Sorbinil-treated control	Sorbinil-treated diabetic
Tension				
n	8	6	5	5
Resting developed tension (g)	0·78 ± 0·05	0·97 ± 0·17	0·73 ± 0·04	0·76 ± 0·09
Maximum developed tension (g)	0·77 ± 0·10	0·26 ± 0·05***	0·41 ± 0·03*	0·24 ± 0·06***
Mean EC50 (nM)	45·4 (31·7–64·9)	6·8 (1·4–33·0)**	12·2 (6·9–21·5)	33·5 (15·9–70·7)†
Rate of tension development ($+dT/dt$)				
Maximum $+dT/dt$ ($g\,s^{-1}$)	30·74 ± 3·87	11·83 ± 1·81***	17·60 ± 1·52*	8·65 ± 2·14***
Mean EC50 (nM)	49·7 (37·2–66·3)	5·1 (1·2–21·8)***	16·0 (11·6–22·1)	41·9 (17·4–100·8)†††
Rate of tension decline ($-dT/dt$)				
Maximum $-dT/dt$ ($g\,s^{-1}$)	19·45 ± 2·84	8·00 ± 0·68**	9·54 ± 0·64**	5·87 ± 1·63***
Mean EC50 (nM)	52·6 (30·0–92·0)	21·3 (3·6–128·4)	17·2 (9·9–29·9)	58·4 (33·3–102·3)

*$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$, compared with control. †$P < 0{\cdot}05$, †††$P < 0{\cdot}001$, compared with atria from untreated diabetic rats. n denotes number of experiments.

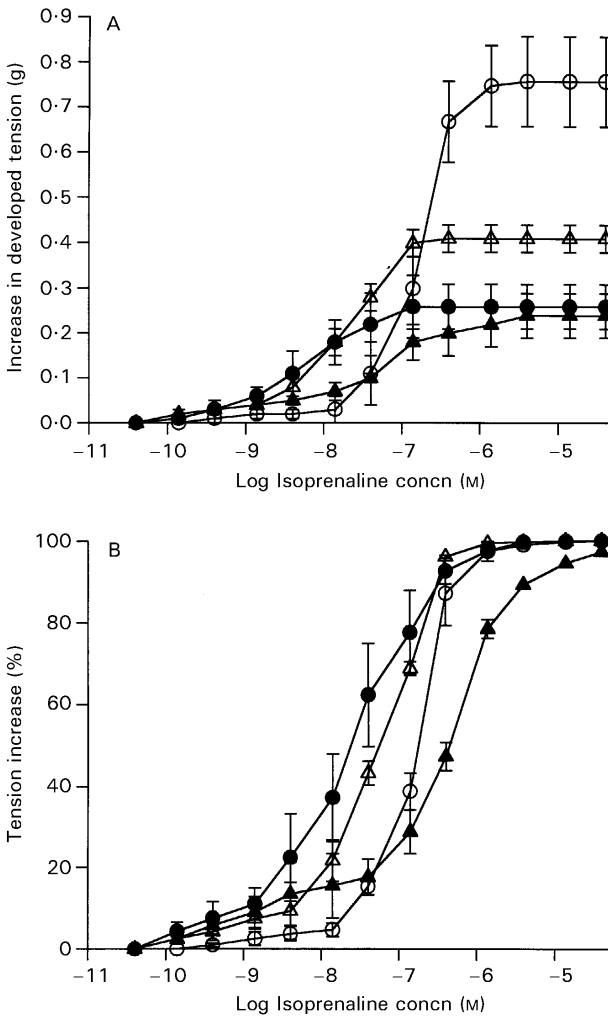

Figure 1. Mean concentration–response curves showing increase in developed tension to isoprenaline of left atria from control (○), diabetic (●), sorbinil-treated control (△) and sorbinil-treated diabetic rats (▲). Mean responses ± s.e.m. are plotted (A) as absolute values in g, and (B) as a percentage of the maximum tension increase.

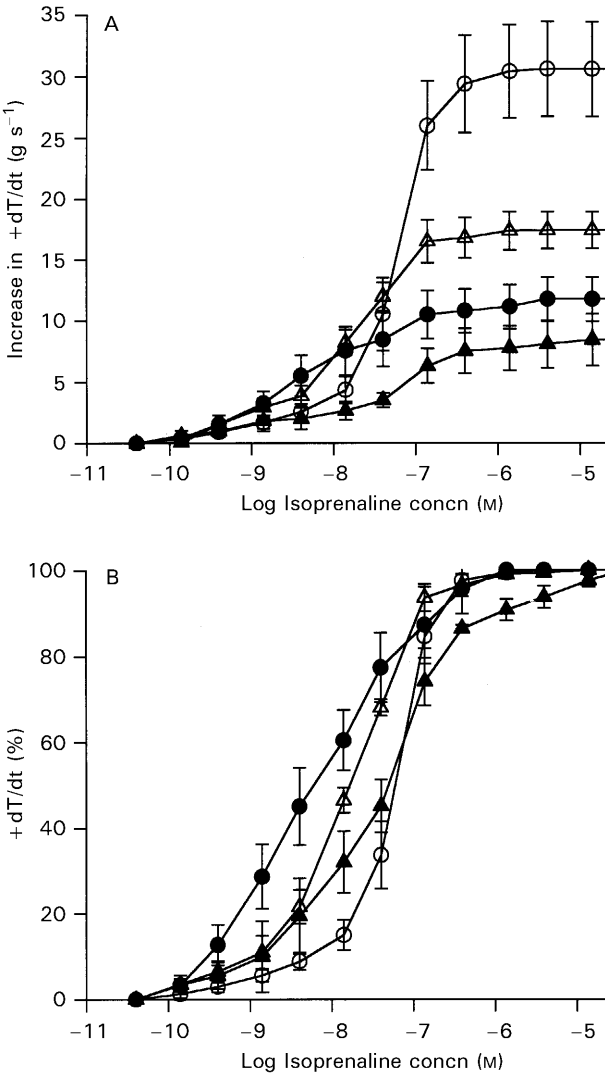

Figure 2. Mean concentration–response curves showing increase in rate of tension development (+dT/dt) to isoprenaline of left atria from control (○), diabetic (●), sorbinil-treated control (△) and sorbinil-treated diabetic rats (▲). Mean responses ± s.e.m. are plotted (A) as absolute values ($g\,s^{-1}$) and (B) as a percentage of the maximum response.

(Table 2, Figure 2). Alterations in −dT/dt almost mirrored these changes, although EC50 values were not significantly different between control and diabetic left atria (Table 2, Figure 3).

α_1-Adrenoceptor-mediated inotropic responses to phenylephrine. The α_1-adrenoceptor agonist phenylephrine had a positive inotropic effect on rat left atria. Maximum developed tension and EC50 values for phenylephrine were not significantly different between control and diabetic tissues (Table 3). Sorbinil treatment had no effect on either parameter in either control or diabetic rats. Similarly, changes in the rates of tension development (+dT/dt) and tension decline (−dT/dt) in response to phenylephrine were not significantly different in control and diabetic left atria. Sorbinil treatment also failed to affect these parameters.

Chronotropic responses of isolated right atria

The resting rate of spontaneously beating right atria was significantly depressed in diabetic rats compared with controls (Table 4). Treatment of diabetic rats with sorbinil failed to prevent this depression and the mean resting rate remained significantly reduced relative to untreated controls. Sorbinil treatment of control rats also resulted in a reduction of the resting rate, producing a resting rate which was significantly lower than in untreated controls.

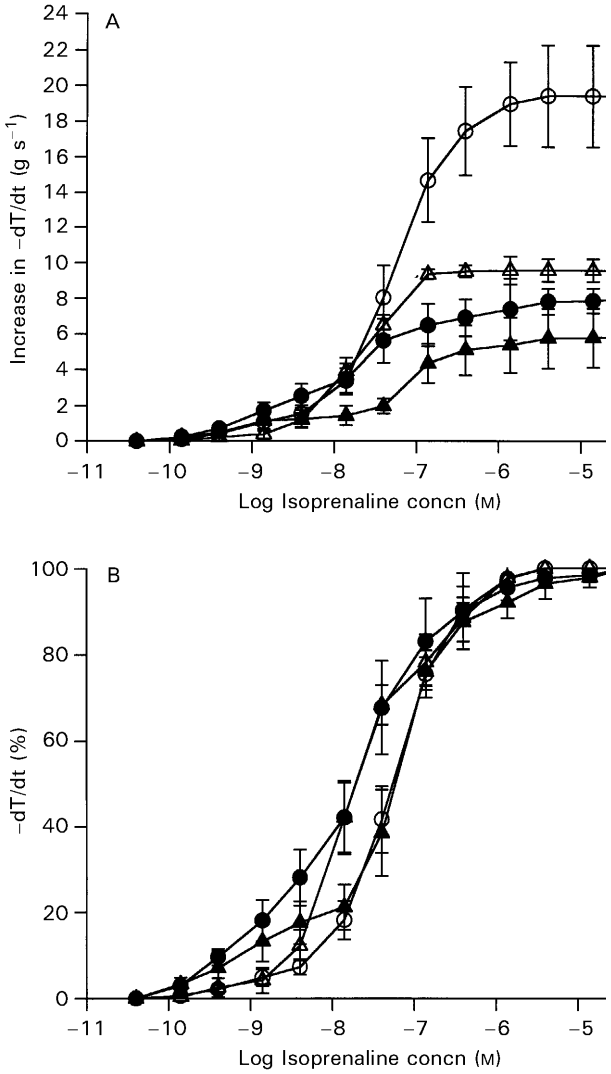

Figure 3. Mean concentration–response curves showing increase in rate of tension decline (−dT/dt) to isoprenaline of left atria from control (○), diabetic (●), sorbinil-treated control (△) and sorbinil-treated diabetic rats (▲). Mean responses ± s.e.m. are plotted (A) as absolute values ($g\,s^{-1}$) and (B) as a percentage of the maximum response.

β-Adrenoceptor-mediated chronotropic responses to isoprenaline. Addition of isoprenaline caused a positive chronotropic response in rat right atria. The maximum rate of increase and EC50 values to isoprenaline were similar in atria from control and diabetic rats (Table 4). Sorbinil treatment had no effect on these parameters in either control or diabetic tissues.

α_1-Adrenoceptor-mediated chronotropic responses to phenylephrine. A positive chronotropic response was found in rat right atria to the α_1-adrenoceptor agonist phenylephrine, although these responses were only small relative to those produced by isoprenaline. The maximum rate increase to phenylephrine was significantly increased in diabetic atria (Table 4). This increase was not prevented by treatment of diabetic rats with sorbinil and indeed the increase was exacerbated by the ARI treatment, with the maximum rate remaining significantly higher than untreated controls. In addition, sorbinil treatment resulted in an increase in the maximum rate response of control atria to phenylephrine, although this was not significant.

Discussion

In this study streptozotocin-induced diabetes in rats resulted in a number of changes in the adrenoceptor-mediated responses of left and right atria. Treatment of diabetic rats with the aldose reductase inhibitor sorbinil prevented only one of these changes—the increased sensitivity of left atria to isoprenaline. Sorbinil treatment also exacerbated some of the diabetes-induced changes and altered some of the adrenoceptor-mediated responses of atria from controls.

Table 3. Geometric mean EC50 values (with 95% confidence limits) and maximum responses (± s.e.m.) for phenylephrine on rat left atria.

	Control	Diabetic	Sorbinil-treated control	Sorbinil-treated diabetic
Tension				
n	5	6	7	7
Maximum developed tension (g)	0·59 ± 0·09	0·31 ± 0·06	0·46 ± 0·06	0·52 ± 0·09
Mean EC50 (μM)	22·5 (2·6–196·1)	7·9 (0·6–114·9)	4·6 (1·3–16·4)	17·9 (4·8–66·8)
Rate of tension development (+dT/dt)				
Maximum +dT/dt ($g\,s^{-1}$)	18·77 ± 3·67	10·95 ± 2·46	17·85 ± 2·44	15·71 ± 3·26
Mean EC50 (μM)	15·1 (2·91–78·2)	1·3 (0·1–132·6)	9·1 (2·5–3·6)	15·5 (4·5–52·9)
Rate of tension decline (−dT/dt)				
Maximum −dT/dt ($g\,s^{-1}$)	10·97 ± 2·19	7·42 ± 1·78	12·16 ± 1·78	9·37 ± 1·86
Mean EC50 (μM)	7·5 (0·9–57·4)	4·5 (0·1–309·9)	5·7 (1·9–17·1)	19·1 (4·2–85·8)

n denotes number of experiments.

Table 4. Geometric mean EC50 values (with 95% confidence limits) and maximum responses (± s.e.m.) for isoprenaline and phenylephrine on rat right atria.

	Control	Diabetic	Sorbinil-treated control	Sorbinil-treated diabetic
Isoprenaline				
n	4	7	7	5
Resting rate (beats min^{-1})	338 ± 15	269 ± 10***	296 ± 7*	241 ± 8***
Maximum rate increase (beats min^{-1})	159·8 ± 23·1	162·9 ± 6·3	191·1 ± 11·7	174·0 ± 7·0
Mean EC50 (nM)	17·5 (4·2–72·4)	8·7 (4·4–17·0)	14·4 (5·5–37·6)	33·2 (8·5–129·1)
Phenylephrine				
n	4	6	5	5
Maximum rate increase (beats min^{-1})	7·3 ± 1·4	32·0 ± 3·4*	24·6 ± 3·7	56·4 ± 10·1***†

*$P < 0.05$, ***$P < 0.001$, compared with control. †$P < 0.05$, compared with untreated diabetic rats. n denotes number of experiments.

Responses of isolated left atria

Left atria from diabetic rats were found to be supersensitive to the β-adrenoceptor agonist isoprenaline, confirming previous reports from our laboratory (Austin & Chess-Williams 1991). Increased β-adrenoceptor-mediated inotropy of cardiac tissues in diabetes has not been well documented, although it has been reported in some short-term diabetic studies (2 weeks (Foy & Lucas 1978) and 3 days (Wald et al 1989)). Short-term type I diabetic patients have also been found to exhibit increased myocardial contractility (Thuesen et al 1985). Thus, an increase in β-adrenoceptor responsiveness or sensitivity may be a characteristic of short-term diabetes.

In this study, the cause of the supersensitive response of left atrial tissues to β-adrenoceptor stimulation is unknown. Treatment of diabetic rats with sorbinil prevented the supersensitivity of left atria to isoprenaline, suggesting that whatever mechanism is operating to cause this supersensitivity, the polyol pathway may be an underlying or contributory factor. This is supported by our previous work (Austin & Chess-Williams 1991) which showed that increased sensitivity of diabetic rat atria to isoprenaline could be prevented by treatment with ponalrestat. It was suggested that the beneficial effects of the aldose reductase inhibitor ponalrestat might be due to a corrective effect on altered calcium handling (Austin & Chess-Williams 1991).

In this study, as well as measuring the tension developed in left atria in response to isoprenaline, we also measured the rate of tension development and decline. Cameron et al (1989) have previously shown that the rate of relaxation of papillary muscle from diabetic rats is affected to a greater extent than the rate of contraction, both of these being slowed by diabetes. However, in our study all parameters appeared to be affected in a similar manner by diabetes.

Responses of isolated right atria

The effect of diabetes on right atrial function was also investigated in this study. The resting rate of the spontaneously beating right atria from diabetic rats was significantly depressed in comparison with that of control tissues, which is in agreement with other reports (Akiyama et al 1989; Schaan et al 1997). Hyperglycaemia is known to alter the electrical activity of the sinoatrial node (Senges et al 1980) and this may account for the observed depression of resting rate. A depression in resting heart rate may act as a protective mechanism in the diabetic state by reducing the energy demand and workload of the myocardium. It appears that the polyol pathway is not involved in this particular alteration since treatment of diabetic rats with sorbinil did not prevent the depressed resting rate. However, the fact that sorbinil exacerbated this reduction suggests that sorbinil has additional effects in these tissues.

Stimulation of right atria with the α_1-adrenoceptor agonist phenylephrine produced positive chronotropic responses, both in control and diabetic rat tissues, in agreement with the findings of Tung et al (1985). These responses were enhanced in right atria from diabetic rats, which is in agreement with the findings of Jackson et al (1986). This supports the theory that α_1-adrenoceptors have a more important role in cardiac function under pathological conditions (Terzic et al 1993). The polyol pathway does not appear to be involved in this change, since treatment with sorbinil failed to prevent the increase. However, the additional effects of sorbinil (i.e., exacerbation of this increase), make reaching a definite conclusion

regarding involvement of the polyol pathway difficult.

β-Adrenoceptor stimulation of right atria with isoprenaline also evoked a positive chronotropic response, which was greater than that induced by α_1-adrenoceptor stimulation. However, this β-adrenoceptor-mediated response was similar in control and diabetic tissues, which agrees with the work of Ramanadam & Tenner (1986), but not that of Durante et al (1989) who reported decreased isoprenaline-induced chronotropy of diabetic atria. These results are in contrast to the altered β-adrenoceptor-mediated inotropic response of left atria from diabetic rats and demonstrate a differential effect on chronotropic and inotropic responses.

Effects of sorbinil treatment

In this study, treatment of diabetic rats with the aldose reductase inhibitor sorbinil prevented only one of the observed changes in adrenoceptor-mediated atrial function—the increased sensitivity of left atria to isoprenaline. The reason for this is unknown. Although other ARIs such as ponalrestat have been reported to be more effective in inhibiting sorbitol formation via the polyol pathway in in-vitro studies (Poulsom 1987), there are reports that sorbinil (a hydantoin ARI) is more potent than the carboxylic acid ARIs such as ponalrestat (Sarges & Petersen 1986). One possible explanation for the ineffectiveness of sorbinil could be the dose of sorbinil administered. However, even very low doses of sorbinil ($2{\cdot}5\,mg\,kg^{-1}$ twice daily), have been found to decrease nerve sorbitol content by 92% (Peterson et al 1979) making it unlikely that the dose of $25\,mg\,kg^{-1}$ daily was insufficient to fully inhibit the polyol pathway. Also, the fact that sorbinil was not totally ineffective and that it had unexpected effects on atrial responses shed doubt on this explanation.

As well as being ineffective in preventing the diabetes-induced changes in atrial function, sorbinil treatment resulted in an exacerbation of some of these changes and caused alterations in control of atrial function which mirrored those induced by diabetes. This suggests that sorbinil has actions in addition to, and independent of, inhibition of the polyol pathway. Spielberg et al (1991) reported that in clinical trials sorbinil is oxidatively metabolised to a potentially harmful intermediate, to which some individuals may be more susceptible, which may lead to a hypersensitivity reaction. In addition, Mauer et al (1989) suggested that sorbinil may produce a mild catabolic state, which could account for their finding of reduced body weight in both control and diabetic rats treated with sorbinil. Sorbinil is also thought to have vasoconstrictor effects (Goldfarb et al 1986) and if it caused hypertension in this study could lead to abnormal cardiac function ex-vivo. Sorbinil was also shown to reduce the availability of arachidonic acid and thus limit the production of vasodilatory prostanoids (Craven & DeRubertis 1989). A possible role for other ARIs as vasoactive agents is supported by the report of Cameron & Cotter (1992) who found that treatment of control rats with an ARI resulted in an enhanced relaxation response of aortae. Austin & Chess-Williams (1991) have also shown that the ARI ponalrestat can increase developed tension in control cardiac tissues and suggested that this agent may augment calcium handling in the heart. Sorbinil was also found to have membrane-associated effects independent of aldose reductase inhibition, and can stimulate Na^+, K^+-ATPase activity in the glomeruli of controls (Cohen & Klepser 1988). If Na^+, K^+-ATPase activity can also be increased in the myocardium by sorbinil, this could explain the increase in α_1-adrenoceptor-mediated responses of right atria.

From our study, it can be concluded that diabetes of 14 days duration has tissue-specific effects on the α_1- and β-adrenoceptor systems within various regions of the rat heart. Sorbinil treatment fails to prevent most of these diabetes-induced alterations in atrial function and has effects on control and diabetic atria which suggest that it may have actions in addition to, and independent of, polyol pathway inhibition. Thus, sorbinil may not be an effective tool for investigation of aldose reductase inhibition within the cardiovascular system.

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