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Endothelial and myogenic regulation of coronary artery tone in the mouse

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Abstract

Ventricular septal (150–200 μm) arteries were isolated from the hearts of six-week-old CD-1 mice and mounted on a pressure myograph. Equilibration of the vessels at 70 mm Hg for 60 min resulted in the development of spontaneous myogenic tone. Maximum tone observed in these vessels greatly exceeded that previously reported in septal arteries from rats. Inhibition of endothelin ET_A and endothelin ET_B receptors with bosentan (1 and 10 μM) reduced basal tone. Endothelin release required intact endothelial cells. The α_1-adrenceptor selective agonists phenylephrine and methoxamine did not cause change in coronary tone, while the α_2-adrenceptor selective agonists 6-allyl-2-amino5,6,7,8-tetrahydro-4*H*-thiazolo-[4,5-d]azepin-dihydrochloride (BHT 920) and clonidine produced vasodilatation. Noradrenaline (1 nM–10 μM) induced a concentration-dependent vasodilatation, which was inhibited by concurrent treatment with yohimbine (10 μM) and propranolol (20 μM). Vasodilatation due to BHT 920 was abolished with vessel denudation, indicating the endothelial location of α_2-adrenoceptors. Acetylcholine (1 nM–10 μM) caused an endothelium dependent vasodilatation; inhibition of nitric oxide synthase with N_ω-nitro-L-arginine methyl ester attenuated this response. The endothelium-dependent vasodilators bradykinin and substance P produced no vasomotor effect in mouse coronary arteries. Differences between human and murine responses may impact on the relevance of the mouse coronary artery for use as a potential model of human coronary vessel diseases.

Keywords: Endothelin; Nitric oxide (NO); Noradrenaline; Smooth muscle, vascular

1. Introduction

The evolution of inbred mouse strains and the recent advent of genetically manipulated mice have made possible the detailed profiling of specific molecular events in a variety of diseases. Although several mouse models of cardiovascular disease are available, there is a surprising paucity of information regarding the physiological and pharmacological properties of the murine coronary artery. Technological advances have facilitated the detailed study of small vessels in vitro; the development of the pressure myograph has allowed for the study of resistance arteries under more physiological conditions as compared to those of the standard wire myograph.

Observations made from studies using large conduit arteries may not be directly applicable to understanding the physiology and pharmacology of resistance arteries (Mulvany and Aalkjaer, 1990). Understanding the properties of resistance arteries from the coronary circulation is paramount, as these vessels regulate blood flow by actively changing vessel tone in response to neural, physical and metabolic stimuli (Ginsburg et al., 1984). In particular, sympathetic stimulation plays an essential role in this modulation, as α-adrenoceptor activation leads to vasoconstriction in most vascular beds, including the coronary circulation in humans (Feigl, 1998). In contrast, adrenoceptor activation can mediate vasorelaxation via endothelial α_2-adrenoreceptors in addition to β-adrenoceptors on vascular smooth muscle (Thorin et al., 1998). Thus, the endothelium can modulate adrenoceptor-mediated vasodilation and represents a form of physiological antagonism (Cocks and Angus, 1983) that has been described in conduit arteries (Hamdad et al., 1996).

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In this study, we characterize the response of the isolated mouse intramyocardial coronary artery to adrenoceptor ligands and acetylcholine receptor ligands, endothelium-dependent vasodilators, and also to changes in intravascular pressure. Our observations may be pertinent to decisions regarding the choice of mice for studies undertaken to mirror human coronary pathophysiology.

2. Materials and methods

2.1. Vessel isolation and cannulation

The isolation and mounting of vessels were performed as previously described (Skarsgard et al., 1997). Briefly, male CD-1 mice (age 6–7 weeks) were administered heparin sulfate (500 U/kg, i.p.) and sodium pentobarbital (30 mg/kg, i.p.) prior to decapitation. The heart was removed and placed in ice-cold physiological salt solution (PSS). The ventricular septal (150–200 μm) arteries were dissected and transferred to an arteriograph filled with oxygenated PSS at 37°C. The vessel was then tied to microcannulae (tip diameter 30–50 μm). Under no flow conditions, the intraluminal pressure was incrementally increased to 70 mm Hg using a pressure servo system (Living Systems, Burlington, VT). Intraluminal diameters were measured using a video edge-detection system and recorded simultaneously onto a personal computer. The vessel was equilibrated for 60 min, whence myogenic tone developed spontaneously. For experiments using endothelium-denuded vessels, a 2-min continuous stream of air bubbles was passed through the lumen after initial development of myogenic tone. One end of the vessel was untied from the microcannula, and air bubbles were forced through the lumen using an air-filled syringe attached to the tubing of the other microcannula. After the endothelium was removed, the vessel was then re-tied to the microcannula and allowed to equilibrate again for 60 min at 70 mm Hg.

2.2. Experimental protocol

In experiments designed to measure the spontaneous myogenic response, pressure–diameter relationships were determined by increasing the intraluminal pressure from 10 to 20 mm Hg, and in 20 mm Hg increments to 120 mm Hg thereafter. At each pressure, a 5-min stabilization period was allowed during which time the vessel typically achieved a steady state diameter. The same protocol was repeated using vessels pre-incubated with 1 or 10 μM bosentan for 30 min. In separate experiments, the concentration dependence of noradrenaline-induced relaxation was determined. Following the development of tone, cumulative additions of noradrenaline (1 nM–10 μM) were made to the PSS.

To investigate adrenoceptor activity, the α_1-adrenoceptor selective agonists phenylephrine and methoxamine were applied to the coronary arteries. In separate experiments, the α_2-adrenoceptor selective agonists BHT 920 and clonidine were also used.

To elucidate, which receptors mediate noradrenaline-induced relaxation, the arteries were incubated with the α_2-adrenoceptor selective antagonist, yohimbine (10 μM), and/or the nonselective β-adrenoceptor antagonist, propranolol (20 μM) for 30 min prior to a noradrenaline (10 μM) challenge. Phenylephrine (10 μM), the α_2-adrenoceptor selective agonist 6-allyl-2-amino5,6,7,8-tetrahydro-4*H*-thiazolo-[4,5-d]azepin-dihydrochloride (BHT 920, 3 μM), and isoprenaline (10 μM) were used as controls before and after the application of an antagonist. BHT 920 (3 μM) and isoprenaline (10 μM) were also applied separately to the endothelium-denuded coronary artery. To determine whether nitric oxide is a possible effector of α_2-adrenoceptor-mediated vasodilatation, arteries were incubated with N^G-nitro-L-arginine methyl ester (L-NAME, 200 μM, 30 min) followed by a BHT 920 (1 μM) or noradrenaline (10 μM) challenge. L-NAME (200 μM) and propranolol (20 μM) were also applied in combination.

Additionally, acetylcholine, both in the presence and absence of L-NAME, was applied cumulatively to the PSS (1 nM–10 μM) and arterial luminal diameter recorded. This protocol was repeated using endothelium-denuded coronary vessels. To study endothelium-dependent vasodilatation, bradykinin and substance P were also applied to the septal arteries.

At the end of each experiment, normal Ca^{2+}-containing PSS was substituted with Ca^{2+}-free PSS to determine passive luminal diameter.

2.3. Expression of results and statistical analysis

Myogenic tone at each pressure was expressed as a percent constriction $= 100\% \times [(D_{\text{Ca-free}} - D_{\text{PSS}})/D_{\text{Ca-free}}]$, where D is the diameter in calcium-free ($D_{\text{Ca-free}}$) or Ca^{2+}-containing PSS (D_{PSS}). Percent relaxation was calculated using the equation $100\% \times [(D_{\text{d}} - D_{\text{b}})/(D_{\text{Ca-free}} - D_{\text{b}})]$, where D is the diameter upon stabilization after drug addition (d), baseline (b) or Ca^{2+} free.

All results are expressed as mean ± S.E.M. of n animals. One vessel segment was obtained from each animal. Statistical evaluation was made using analysis of variance (ANOVA), and means were considered significantly different when $P < 0.05$.

2.4. Solutions and chemicals

The composition of the PSS was (in mM): NaCl 119, KCl 4.7, KH_2PO_4 1.18, $NaHCO_3$ 24, $MgSO_4 7H_2O$ 1.17, $CaCl_2$ 1.6, glucose 5.5 and EDTA 0.026. Ca^{2+}-free solution was a PSS solution containing no $CaCl_2$ and 2.0 mM EGTA. The composition of 80 mM high K^+ solution

was: NaCl 2.279, KCl 5.965, KH_2PO_4 0.1606, $MgSO_4$ 0.1409, $NaHCO_3$ 2.092, and 0.006 EDTA. BHT 920 HCl (6-allyl-2-amino5,6,7,8-tetrahydro-4*H*-thiazolo-[4, 5-d]azepin-dihydrochloride) was supplied by Boehringer Ingelheim Canada (Ontario). Bosentan (4-*tert*-butyl-*N*-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2,2′-bipyrimidin-4-yl] benzene sulfonamide monohydrate) was from Actelion , Switzerland. All other drugs were purchased from Sigma (St. Louis, MO).

3. Results

3.1. Basal tone of mouse septal arteries

Septal arteries developed basal tone in normal PSS. Spontaneous tone developed upon equilibration at 70 mm Hg for 1 h. Step increases in pressure from 10 to 20 mm Hg, then from 20 to 120 mm Hg in 20-mm Hg increments led to the development of myogenic tone at 60 mm Hg ($n = 4$), manifested by a pressure-induced decrease in luminal diameter (Fig. 1A). Thus, increases in pressure lead to constriction of the arteries in normal PSS (Fig. 1B). Vessel tone was present at pressures as low as 20 mm Hg. Between 60 and 120 mm Hg, vessel constriction was between 61%and 65% ($n = 4$). Spontaneous rhythmic activity was not seen in any of the arteries. In the presence of 1 μM bosentan, vessel tone decreased and vasoconstriction was calculated to be between 43% and 45% ($n = 4$, Fig. 2). With incubation of the vessels with 10 μM bosentan, myogenic tone was further decreased, with vessel constriction between 29% and 33% at 60–120 mm Hg ($n = 4$–5, Fig. 2). In endothelium-denuded vessels, incubation with 10 μM bosentan resulted in similar vessel constriction of 20–26% at 80–120 mm Hg ($n = 4$) as in control tissues (19–26%, $n = 4$, Fig. 3). Vasoconstriction due to 80 mM

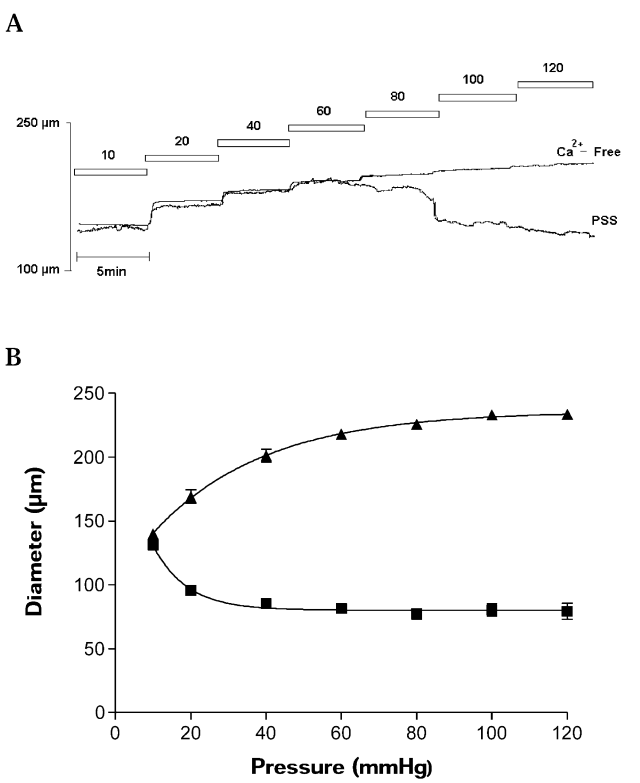

Fig. 1. (A) Trace recording of arterial diameter in normal Ca^{2+}-containing PSS and Ca^{2+}-free PSS. In normal PSS, spontaneous myogenic tone develops at 60 mm Hg. In Ca^{2+}-free PSS, tone is absent and the vessel displays passive behavior. (B) The relationship between intraluminal pressure and vessel diameter in normal PSS and Ca^{2+}-free PSS. In normal PSS, increases in pressure lead to a decrease in vessel diameter. Between 60 and 120 mm Hg, luminal diameter measured between 79.3 ± 6.2 and 81.5 ± 3.2 μm (■, $n = 4$). In Ca^{2+}-free PSS, increases in pressure lead to vasodilatation. Between 60 and 120 mm Hg, luminal diameter measured between 217.9 ± 3.3 and 233.5 ± 3.2 μm (▲, $n = 4$).

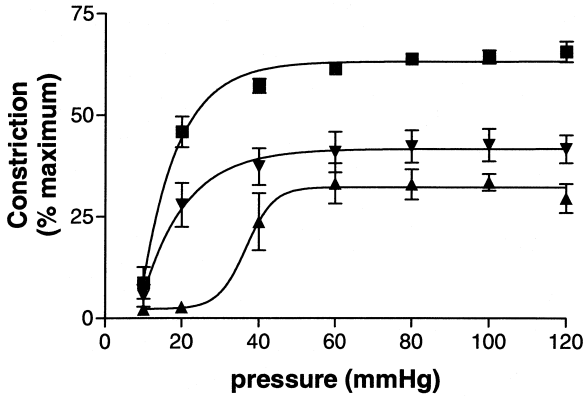

Fig. 2. Development of spontaneous myogenic tone in mouse septal arteries. Intraluminal pressure was increased from 10 to 20 mm Hg, then from 20 to 120 mm Hg in 20-mm Hg increments. The vessel was allowed to equilibrate for 5 min at each pressure. Between 60 and 120 mm Hg, vessel constriction in normal PSS was 61–65% (■, $n = 4$). In the presence of 1 μM bosentan (▼), vessel constriction within this pressure range was 40–42% ($n = 4$). In addition, the presence of 10 μM bosentan (▲), vessel constriction was 29–33% ($n = 4$).

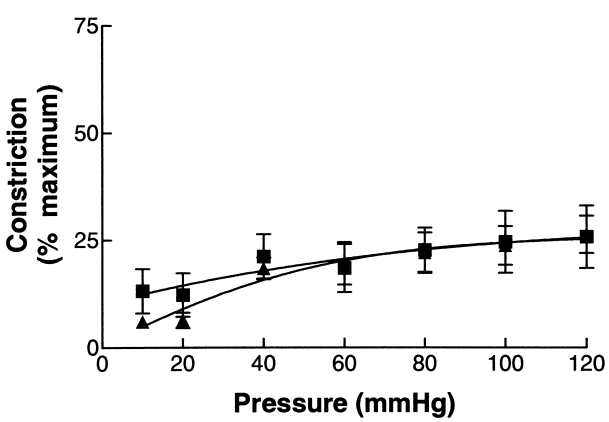

Fig. 3. Development of spontaneous myogenic tone in endothelium-denuded mouse septal arteries. Between 60 and 120 mm Hg, vessel constriction in normal PSS was 19–26% (■, $n = 4$). In the presence of 10 μM bosentan (▲), vessel constriction within the same pressure range was 20–26% ($n = 4$).

K^+ solution was used as a control for any non-specific effect of bosentan (10 μM); constriction to K^+ was unaffected by bosentan (unpublished data). Tone was abolished when normal Ca^{2+}-containing PSS was substituted with Ca^{2+}-free PSS, whence step increases in intraluminal pressure only dilated the vessels ($n = 4$, Fig. 1A,B).

3.2. Effect of acetylcholine

Acetylcholine (1 nM–10 μM) caused concentration-dependent vasodilation in septal arteries possessing basal tone ($n = 3$–9, Fig. 4). At the threshold concentration of 1 nM acetylcholine, there was a detectable relaxation of 0.2 ± 0.1% (% maximum response, $n = 5$). At the highest studied concentration (10 μM), acetylcholine produced 65.3 ± 10.3% relaxation ($n = 3$). Relaxation induced by 10 μM acetylcholine was abolished by pre-treatment with 200 μM L-NAME ($n = 5$). In endothelium-denuded arteries, acetylcholine (10 μM) elicited no vasodilatory response.

3.3. Endothelial α_2-adrenoceptors and noradrenaline

There was no vascular response to either of the α_1-adrenoceptor selective agonists phenylephrine or methoxamine (unpublished data). In comparison, both agents caused concentration-dependent vasoconstriction in size-matched mouse mesenteric arteries (unpublished data).

The α_2-adrenoceptor agonist clonidine (1 and 10 μM, respectively) caused 22.1 ± 3.1% and 33.5 ± 3.3% relaxation of arteries possessing basal tone ($n = 4$, Table 1). Another α_2-adrenoceptor agonist, BHT 920 (1 μM), chosen near its EC_{50} in rabbit femoral arteries (Garcia-Villalon et al., 1992), caused 25.8 ± 3.7% relaxation of arteries ($n = 5$, Table 1). This response to BHT 920 was abolished after incubation with either 10 μM yohimbine ($n = 7$, Table 2) or 200 μM L-NAME ($n = 5$).

Table 1
Effect of various α- and β-adrenoceptor ligands on septal arteries pressurized at 70 mm Hg. Concentrations used: BHT 920 = 1 μM; isoprenaline; noradrenaline; prazosin; yohimbine = 10 μM; propranolol = 20 μM

Treatment	Relaxation (% maximum)
Clonidine (1 μM)	22.1 ± 3.1 ($n = 4$)
Clonidine (10 μM)	30.5 ± 3.3 ($n = 3$)
BHT 920	25.8 ± 3.7 ($n = 5$)
BHT 920 + yohimbine	No response
Isoprenaline	82.2 ± 1.0 ($n = 5$)
Isoprenaline + yohimbine	77.3 ± 10.2 ($n = 4$)
Noradrenaline	86.5 ± 3.0 ($n = 5$)
Noradrenaline + yohimbine	37.5 ± 3.0 ($n = 5$)
Noradrenaline + propranolol	83.1 ± 8.4 ($n = 5$)
Noradrenaline + prazosin + propranolol	45.0 ($n = 2$)
Noradrenaline + yohimbine + propranolol	No response

In septal arteries with basal tone, noradrenaline caused concentration-dependent (1 nM–10 μM) relaxation ($n = 5$, Fig. 5), with a maximum response of 86.5 ± 3.0% ($n = 5$). A 10-μM yohimbine was partially effective in reducing the response to a single noradrenaline (10 μM) challenge (37.5 ± 3.0%, $n = 5$). Arterial incubation with L-NAME (200 μM) resulted in a slight inhibition of noradrenaline (10 μM)-induced vasodilatation (79.7 ± 8.7%, $n = 3$). In arteries pre-incubated with both prazosin (10 μM) and propranolol (20 μM), noradrenaline (10 μM) produced 45.0% relaxation ($n = 2$, Table 1).

In pressurized endothelium-denuded arteries, neither acetylcholine (10 μM) nor BHT 920 (3 μM) elicited vasodilatory responses.

3.4. Smooth muscle β-adrenoceptors and noradrenaline

A 10-μM isoprenaline caused vasodilatation (82.2 ± 1.0%, $n = 5$), which was antagonized by 20 μM propra-

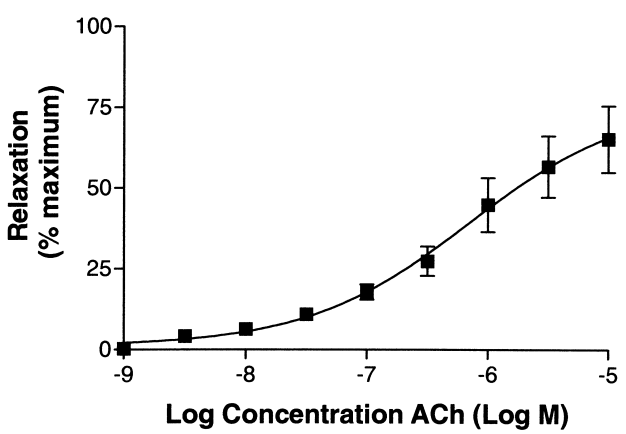

Fig. 4. Acetylcholine (ACh)-induced concentration-dependent relaxation of septal arteries pressurized at 70 mm Hg. Acetylcholine was cumulatively applied to the bath. The vessel was allowed to reach steady state within a 5-min period prior to subsequent acetylcholine addition.

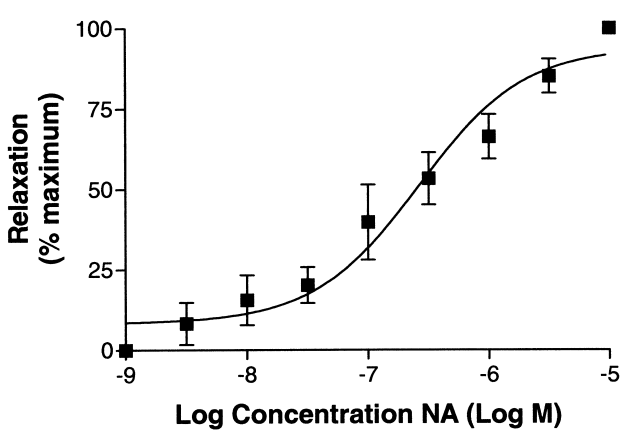

Fig. 5. Noradrenaline (NA)-induced concentration-dependent relaxation of septal arteries pressurized at 70 mm Hg ($n = 5$). Noradrenaline was cumulatively applied to the bath. The vessel was allowed to reach steady state within a 5-min period prior to subsequent noradrenaline addition.

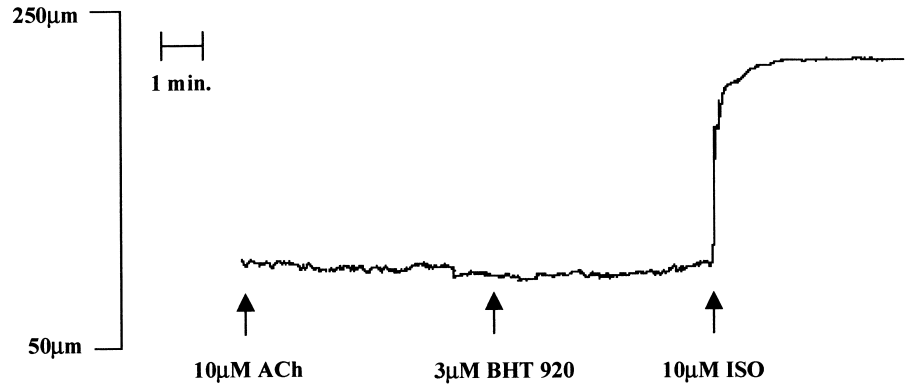

Fig. 6. Trace recording of endothelium-denuded septal arterial diameter. The vessel was pressurized at 70 mm Hg. Both a 10-μM acetylcholine challenge and a 3-μM BHT 920 challenge produced no effect. A 10-μM isoprenaline caused vasodilatation.

nolol ($n = 5$), but unaffected by 10 μM yohimbine (77.3 ± 10.2%, $n = 4$, Table 1). In endothelial-denuded arteries, isoprenaline (10 μM) also induced vasorelaxation (Fig. 5).

In septal arteries pressurized at 70 mm Hg, propranolol (20 μM) did not significantly reduce the response to noradrenaline (10 μM, 83.1 ± 8.4%, $n = 5$). Combination of propranolol (20 μM) and yohimbine (10 μM) abolished the response to 10 μM noradrenaline ($n = 6$, Table 2). In addition, the combination of propranolol (20 μM) and L-NAME (200 μM) abolished the response to 10 μM noradrenaline (0.2 ± 1.2%, $n = 4$) (Fig. 6).

3.5. Endothelium-dependent vasodilators

The endothelium-dependent vasodilators bradykinin and substance P were applied to pressurized arteries. Neither bradykinin (10 μM) nor substance P (0.1 μM) produced any vasodilator effect.

4. Discussion

The mouse is routinely used as a model system to assess cardiovascular diseases, such as atherogenesis (Keidar et al., 1999), thrombosis (Fujihira et al., 1993), myocardial infarction (Harada et al., 1999), chronic heart transplant rejection (Koglin and Russell, 1999), myocarditis (Carthy et al., 1998) and cardiotoxicity (Rosenoff et al., 1975). The first successful genetic manipulation in the mouse in the early 1980s and the eventual ease of recombinant DNA technology naturally made it an animal of choice for modeling of human disease. However, the validity of the mouse model in assessing human pathophysiology has not been evaluated. Although mice and humans share highly conserved genes that regulate fundamental aspects of cardiovascular morphogenesis (Chien, 1996), there may still be important variability in physiological regulation and responses. For example, it has been reported that the coronary circulation of small animals may not be optimal in the study of coronary angiogenesis and revascularization, due to extensive collateralization (Chien, 1996). Uncertainties about the vasoregulatory states of murine intramural coronary arteries and the applicability of the mouse for modeling abnormalities hypothesized in human hearts, served as a foundation for our observations.

The blood pressure of the mouse is reported to be in the vicinity of 90–100 mm Hg (Wang et al., 1997). Our study demonstrated that the mouse septal artery possessed a relatively high degree of myogenic tone within this pressure range. In comparison to the male rat septal artery where maximal tone is between 30% and 40% constriction (Wellman et al., 1996; Skarsgard et al., 1997), basal tone in the mouse septal artery is approximately twofold greater. The blockade of endothelin receptors by bosentan significantly decreased the extent of basal tone, indicating that in the mouse coronary circulation, endothelin is an important regulator of diameter and hence coronary flow. Addition of bosentan to de-endothelialized arteries did not alter the extent of myogenic tone (compared to control vessels untreated with bosentan), indicating that basal release of endothelin occurs from endothelial cells. The target for endothelin is endothelin receptors located in smooth muscle cells of the media.

Noradrenaline produced a α_2- and β-adrenoceptor-mediated, concentration-dependent relaxation in the mouse coronary resistance artery. Inhibition of nitric oxide synthase with L-NAME attenuated the vasodilatory response to the selective α_2-adrenoceptor ligand BHT 920, thus suggesting that this response is mediated by nitric oxide. These results are in agreement with Thorin et al. (1998) who reported that α_2-adrenoceptor-mediated relaxation in mesenteric arteries of mice could be antagonized by nitric oxide synthase inhibition. Furthermore, since BHT 920 elicited no response in the endothelium-denuded artery, it was concluded that the α_2-adrenoceptors of the mouse coronary artery were endothelium-located.

The concentration of noradrenaline in the coronary circulation at rest is approximately 1.2 nM (Hjemdahl and

Linde, 1983). This same concentration of noradrenaline is reported to cause α_1- and α_2-adrenoceptor mediated constriction in the isolated human coronary artery, even in the absence of β-blockade (Saetrum Opgaard and Edvinsson, 1997). However, we demonstrate that in the isolated mouse coronary artery, not only is there is a lack of α_1-adrenoceptor response, but noradrenaline (1 nM–10 μM) consistently caused vasodilatation; both mark important phenotypic species differences in the pharmacology of the coronary circulation.

Our study also demonstrated that the mediation of acetylcholine-induced vasodilatation in the mouse coronary occurred via endothelium-derived nitric oxide, as confirmed by the lack of response to acetylcholine in the presence of L-NAME or absence of endothelium. This mechanism of acetylcholine action is similar to that in the isolated human coronary artery. Paradoxically, in human coronary microvessels (Angus et al., 1991) (non-septal) and epicardial vessels (Kalsner, 1985), variable populations of acetylcholine receptors may also exist on the medial smooth muscle, mediating vasoconstriction, countering the role of those on the endothelium, which mediate vasorelaxation.

Lastly, the endothelium-dependent vasodilators bradykinin and substance P were found to be inactive in the mouse coronary arteries. In contrast, bradykinin has been reported to relax the coronary arteries of various species including human and dog (Regoli and Barabe, 1980). Substance P is also a coronary artery vasorelaxant in the human (Tousoulis et al., 1999), as well as in swine (Uchida et al., 1999).

In conclusion, the present study elucidated responses of the pressure myograph-mounted mouse coronary artery to pharmacological agents of pertinence to those previously reported in the human coronary artery. Briefly, the isolated mouse septal artery possessed a high degree of myogenic tone to which endothelin contributed significantly. These coronary arteries relaxed to noradrenaline via (endothelium-located) α_2- and (smooth muscle-located) β-adrenoceptors, as well as to acetylcholine via endothelium-derived nitric oxide. However, α_1-adrenoceptor selective agonists as well as bradykinin and substance P were found to have no vasoactive effect. Differences between human and murine responses illustrated by these findings may impact on the relevance of the mouse coronary artery as a potential model of human coronary vessel diseases.

Acknowledgements

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