Critical Role for the α-1B Adrenergic Receptor at the Sympathetic Neuroeffector Junction

Seth A. Townsend, Albert S. Jung, Yen Shi Gillian Hoe, Rafael Y. Lefkowitz, Shakil A. Khan, Christopher A. Lemmon, Robert W. Harrison, KwangHo Lee, Lili A. Barouch, Susanna Cotecchia, Artin A. Shoukas, Daniel Nyhan, Joshua M. Hare, Dan E. Berkowitz

Abstract—The α-1 adrenergic receptors (α1ARs) are critical in sympathetically mediated vasoconstriction. The specific role of each α1AR subtype in regulating vasoconstriction remains highly controversial. Limited pharmacological studies suggest that differential α1AR responses may be the result of differential activation of junctional versus extrajunctional receptors. We tested the hypothesis that the α1BAR subtype is critical in mediating sympathetic junctional neurotransmission. We measured in vivo integrated cardiovascular responses to a hypotensive stimulus (induced via transient bilateral carotid occlusion [TBCO]) in α1AR knockout (KO) mice and their wild-type (WT) littermates. In WT mice, after dissection of the carotid arteries and denervation of aortic baroreceptor buffering nerves, TBCO produced significant pressor and positive inotropic effects. Both responses were markedly attenuated in α1BAR KO mice (change systolic blood pressure 46±8 versus 11±2 mm Hg; percentage change in the end-systolic pressure-volume relationship [ESPVR] 36±7% versus 12±2%; WT versus KO; P<0.001). In vitro α1AR mesenteric microvascular contractile responses to endogenous norepinephrine (NE; elicited by electrical field stimulation 10 Hz) was markedly depressed in α1BAR KO mice compared with WT (12.4±1.7% versus 21.5±1.2%; P<0.001). In contrast, responses to exogenous NE were similar in α1BAR KO and WT mice (22.4±7.3% versus 33.4±4.3%; NS). Collectively, these results demonstrate a critical role for the α1AR in baroreceptor-mediated adrenergic signaling at the vascular neuroeffector junction. Moreover, α1BARs modulate inotropic responses to baroreceptor activation. The critical role for α1B AR in neuroeffector regulation of vascular tone and myocardial contractility has profound clinical implications for designing therapies for orthostatic intolerance. (Hypertension. 2004;44:776-782.)

Key Words: receptors, adrenergic alpha ■ hypotension ■ sympathetic nervous system ■ vasoconstriction

Functional studies with subtype-selective antagonists as well as differential mRNA studies suggest that different α-1 adrenergic receptor (α1AR) subtypes mediate contractile function in different vessel beds1 and in arteries versus veins.2 Use of specific adrenergic receptor knockout (KO) mice has also been useful in defining the role of α1AR subtypes in cardiovascular regulation.3–6 However, results in KO mice remain controversial, with each subtype contributing to regulation of blood pressure and vascular contractility but without a subtype-selective role being clearly apparent. The α1A, B, and D AR subtypes have been shown to contribute to the maintenance of basal blood pressure and vasopressor responses to exogenous agonists. Specifically, α1A and α1D AR KO mice have lower basal blood pressure, whereas all 3 KO mice models have attenuated pressor responses to exogenous norepinephrine (NE). However, it is becoming increasingly appreciated that differential α1AR-mediated responses may be the result of different receptor subtypes at junctional versus extrajunctional sites.7–9 Thus, a critical and clinically relevant question in α1AR adrenergic biology remains: is there a specific receptor subtype that mediates sympathetic transmission at the neuroeffector junction?10

Clinical data suggest that orthostatic intolerance (OI) may result when α1BARs are specifically inhibited.11 Thus, we hypothesized that the α1B AR is the subtype critical in mediating vasoconstriction at the neuroeffector junction. To test the hypothesis, we measured integrated cardiovascular responses to selective carotid arterial baroreceptor unloading induced by transient bilateral carotid occlusion (TBCO) in mice with a homozygous deletion of the α1B AR gene. We also determined the vascular contractile responses in mesenteric resistance vessels in vitro to endogenous NE (mediated by electrical field stimulation [EFS]) in KO and wild-type (WT) mice.

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This work was presented in part at the American Heart Association meeting in Anaheim, Calif, in 2001.
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Methods

Murine Species
Nineteen α1AR−/− mice and 14 of their WT controls between 2 and 5 months of age were used in the study. The generation of the α1AR KO mice has been described previously.3 Mice were housed under diurnal lighting conditions and allowed food and tap water ad libitum. Animal treatment and care was provided in accordance with institutional guidelines, and the protocol was approved by the animal care and use committee of the Johns Hopkins University School of Medicine.

In Vivo–Integrated Cardiovascular Responses to Endogenous Sympathetic Activation

Carotid Artery Isolation, Isolation, and Sectioning of Aortic Depressor Nerve and Sympathetic Trunk
Anesthesia was initiated with brief isoflurane inhalation followed by intraperitoneal injection of urethane (750 mg/kg), morphine (0.6 mg/kg), and etomidate (5.6 mg/kg) dissolved in deionized water. Supplemental intraperitoneal anesthesia (one-fifth dose) was provided if needed so the animals remained unresponsive to tail pinch by forceps, as assessed by changes in heart rate (HR) and blood pressure. Temperature was measured with a rectal probe and maintained at ∼37°C. Animals were intubated with a blunt 19-gauge needle via a tracheotomy and were ventilated with a custom-designed constant-pressure ventilator with 100% oxygen at 120 breaths per minute and a tidal volume of 200 μL.

The cervical region was exposed via a midline ventral incision, the right and left thyroid lobes were retracted, and the sternomastoid muscles were retracted bilaterally. The sternohyoïd was looped with 6.0 silk and retracted over the trachea to expose the common carotid sinus and artery region. Carotid arteries parallel to the trachea were carefully isolated. Afferent signals from the aortic arch baroreceptors were eliminated by bilaterally sectioning the aortic depressor nerve (ADN) and the sympathetic trunk (ST). To measure open-loop baroreceptor responses, selective arterial baroreceptor unloading was induced by transient occlusions of both carotid arteries (TBCO) for 10 to 15 seconds. The afferent neural signal in this protocol is generated by a decrease in blood pressure sensed by the carotid baroreceptors, distal to the point of carotid occlusion. The efferent response including blood pressure, HR, and myocardial contractility are then measured. However, the presence of baroreceptors in the aortic arch and heart, which lie proximal to the point of occlusion, will not sense a decrease in arterial pressure and will thus be capable of buffering the cardiovascular effector responses, hence the need for aortic arch baroreceptor deafferentation. The relative location of the ADN and ST has been published previously.12 The ST is located directly adjacent to the vagus nerve and is much larger in diameter than the ADN. The ADN is delicate and small in diameter and is located in between the trachea and the vagus nerve, closely adherent to the ST or wrapping under and over the carotid artery.

Placement of Combined Micromanometric/Conductance Catheter and Measurement of Pressure–Volume Loops With TBCO
The chest was entered through an anterior thoracotomy under a dissecting microscope, and a small apical stab was made at the left ventricle (LV) apex, leaving the pericardium partially intact. The conductance catheter (Millar 1.4-Fr; SPR-671) was then advanced retrograde into the LV along the cardiac longitudinal axis with the distal tip in the aortic root and proximal electrode just within the endocardial wall of the LV apex.

With the catheter(s) fixed in place, baseline values and responses to inferior vena cava (IVC) occlusions were recorded. These values were recorded again after the carotid arteries were bilaterally occluded and the transient cardiovascular responses reached an equilibrium level (usually 10 to 15 seconds). Recordings were performed twice.

Pressure–Volume Loop Data Analysis
Indices of myocardial systolic and diastolic performance were derived from pressure–volume (PV) data obtained at steady state and during transient unloading (vena caval occlusion [VCO]) of the heart. VCO was performed by rapid (1 to 2 seconds) complete compression of IVC with small forceps, during which a series of PV loops were recorded. Baseline and VCO readings were acquired for TBCO and non-TBCO states for WT and α1AR KO mice. VCO-mediated acute preload reduction allows the end-systolic PV relationship (ESPVR). Myocardial contractility can be indexed by the peak rate of rise in LV pressure divided by instantaneous pressure (dP/dt-IP)13 and by the load-independent parameter end-systolic elastance (Ees).14 Ees is the slope of the ESPVR. Although the ESPVR is nonlinear in mice, over the range of the data obtained by preload and afterload changes, the ESPVR can be considered linear.15 End systole is measured as the point at peak elastance (peak P/V ratio). A linear regression line is then fit through these points and the slope derived.

Baseline cardiac preload was indexed as the left ventricular end-diastolic volume (EDV) and end-diastolic pressure. Cardiac afterload was evaluated with effective arterial elastance (Ea; ratio of LV systolic pressure to stroke volume).16 This parameter is not preload dependent and has been validated to closely approximate total afterload, which incorporates systemic vascular resistance, aortic impedance, and the reflected wave properties of the vasculature. Systemic vascular resistance (Svr) is calculated as follows: Svr = mean arterial pressure [MAP]−right atrial pressure [RAP]/CO. Cardiac output can be calculated as the product of HR and stroke volume from PV loops. An estimate of MAP is derived from PV loop data and estimates of RAP from known measurements in mice. In this way, an estimate of Svr is made. Tau ln represents the time constant for relaxation, an accurate measure of diastolic function. We have used Tau ln, the time constant of relaxation derived from the monoeponential equation describing the rate of fall of ventricular pressure. This is a well-validated measure of the rate of diastolic relaxation.17

Mesenteric Microvessel Studies
A mesenteric resistance artery (diameter ∼180 to 250 μm) was separated from the surrounding connective tissue and mesenteric vein in a HEPES physiological salt solution (PSS; in mmol/L buffer [135.5 NaCl, 5.9 KCl, 1.2 MgCl2, 11.6 HEPES, 11.5 glucose, and 2.2 CaCl2, and was adjusted to a pH of 7.4]) on ice. Arteries were mounted on a dual-pipette pressure servo system (model PS/200Q; Living Systems) at a constant static pressure of 60 mm Hg. The isolated vessel was superfused with HEPES and maintained at 37°C by an inline heater (SH-27B; Warner). The lumen of the vessel was perfused with HEPES PSS (as above). External vessel diameter was monitored and recorded using a videodimension analysis system (Ion-Optix Myocam). An electric stimulator (Grass SD9) and electrodes were used to establish an AC through the perfusion bath. The sympathetic nerves of the isolated vessel were field stimulated at 80 V, which represented a current of ∼200 mA. The pulse duration was 5 ms, and the pulse train length was ∼25 to 50 seconds (the time taken for the response to plateau). A dose response to NE was applied to the perfusion system at concentrations of 0.01 to 10 μmol/L in one half log doses. In the electrical stimulation and the NE dose response, the vessel diameter reached a stable plateau at which point the vessel diameter was measured. This protocol was then repeated in the presence of 1 to 10 μmol/L prazosin.

Statistical Analysis
All data are presented as mean±SEM, with N being indicated for each experimental protocol. Statistical analyses were performed using unpaired Student t tests. A value of P<0.05 was considered significant. For dose-response curves, NE dose responses in mesen-
**Table 1.** Baseline Hemodynamics in WT and α₁bAR KO Mice

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>WT</th>
<th>α₁bAR KO</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120±2</td>
<td>111±3</td>
<td>0.04*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>666±7</td>
<td>652±19</td>
<td>0.6</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea (mm Hg/μL)</td>
<td>9±0.3</td>
<td>5±0.4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Svr (dynes·sec·cm⁻²)</td>
<td>868±36</td>
<td>568±58</td>
<td>0.0013*</td>
</tr>
<tr>
<td>Preload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>6±0.79</td>
<td>5.5±0.025</td>
<td>0.5</td>
</tr>
<tr>
<td>EDV (μL)</td>
<td>26±1.3</td>
<td>57±8</td>
<td>0.006*</td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dP/dt (mm Hg per second)</td>
<td>17 660±818</td>
<td>14 564±862</td>
<td>0.02*</td>
</tr>
<tr>
<td>dP/dt-IP (s⁻¹)</td>
<td>147±6</td>
<td>130±6</td>
<td>0.07</td>
</tr>
<tr>
<td>Ees (mm Hg/μL)</td>
<td>11±5</td>
<td>8±2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Diastole**

| Tau (ms)                | 4±0.09| 4±0.15  | 1.0     |

Data are mean±SEM; P values as reported using t test; *<0.05. EDP indicates end-diastolic pressure.

**Results**

**Effect of α₁bAR Deletion on Baseline Hemodynamic Data**

We used a combined micromanometer conductance catheter to assess the determinants of cardiovascular performance in WT and α₁bAR KO mice (Table 1). In anesthetized instrumented mice, baseline HR was similar in α₁bAR KO mice and WT. In contrast, systolic blood pressure (SBP) and Ea were significantly lower, and LV chamber volume was significantly higher in the α₁bAR KO mice compared with WT (Table 1). Moreover, myocardial contractility was lower, as reflected by dP/dt. The baseline dP/dt-IP was also lower and demonstrated a trend toward significance (Table 1).

**Effect of Selective Carotid Arterial Baroreceptor Unloading (TBCO) on Hemodynamic Parameters**

To assess the hemodynamic responses to a hypotensive stimulus, both carotid arteries were transiently occluded (~10 to 15 seconds), after denervation of ADN and ST. These nerves are sectioned to prevent buffering of the responses by baroreceptors in the aortic arch. TBCO thus represents an open-loop baroreflex stimulus. PV loop data were then collected after transient IVC occlusion. As shown in Table 2 and Figure 1, TBCO produced a significant pressor response (33±5% increase in SBP) in WT mice, consistent with intact baroreflex reactivity. In contrast, the pressor response was markedly attenuated in α₁bAR KO mice (9±2% increase in SBP; P<0.001 versus WT). Although there was a small increase in HR after TBCO in WT mice (2±0.4%), there was a decrease in α₁bAR KO mice (~2±0.7%; P=0.001 versus WT). TBCO stimulated enhanced myocardial contractility in WT mice (Table 2; Figure 1). Because TBCO is associated with significant changes in loading, the best load-independent measure of contractility (Ees) was used to assess the changes observed in contractility. There was a significant increase in the slope of the ESPVR (Ees) in WT mice (70±16%) after TBCO (Table 2; Figure 1). In marked contrast, TBCO resulted in minimal increase in contractility in α₁bAR KO mice (7±12%; P<0.01 versus WT). Most important, there was a significant increase in Ea in WT mice after TBCO, which was markedly attenuated in KO mice (Table 2).

**Mesenteric Vascular Responses to Endogenous (Periarterial EFS) and Exogenous NE**

The profound attenuation in pressor responses to endogenous sympathetic activation in α₁bAR KO mice prompted us to examine the in vitro vascular responses to endogenous and exogenous NE. There was no significant difference in the size of the mesenteric microvessels in WT and α₁bAR KO mice (239±25 mm versus 227±25; WT versus KO; NS). Isolated, pressurized mesenteric microvessels were stimulated with periarterial platinum electrodes (to release endogenous neurotransmitters such as NE) or exogenous-applied NE. Electrical stimulation (2 to 10 Hz) resulted in a significant frequency-dependent reduction in vessel diameter (Figure 2). This response was markedly inhibited by the nonspecific α₁AR antagonist prazosin. For example, in WT at 10 Hz, the vasoconstrictor response was decreased from 19.5±1.1% to 11.8±0.5% by prazosin (n=4 to 7; 10 Hz; WT versus WT+prazosin; P<0.001). This suggests that a significant component of the vasoconstrictor response is mediated by α₁ARs, whereas the remainder is mediated by nonadrenergic co-transmitters (possibly neuropeptide Y and ATP).18 In marked contrast to the WT vessels, there was a profound reduction in the response to 10 Hz EFS in the α₁bAR KO mouse vessels (19.5±1.1% versus 9.1±1.1%; WT versus α₁bAR KO; n=7 to 9; P<0.001). No difference could be observed between the non-α₁AR-inhibitable portion of the responses in WT and KO mice (11.8±0.5% versus 9.1±1.1%; WT+prazosin versus α₁bAR KO; NS; Figure 2). Moreover, prazosin had no significant further effect on the response to EFS in α₁bAR KO vessels (9.1±1 versus 8.7±1.9%; α₁bAR KO versus α₁bAR KO+prazosin; NS).

**Table 2.** Change in Hemodynamic Parameters From Baseline After ~15 Seconds of TBCO (Percentage Change)

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>Percentage (WT)</th>
<th>Percentage (α₁bAR KO)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>33±5</td>
<td>9±2</td>
<td>0.0002*</td>
</tr>
<tr>
<td>HR</td>
<td>2±0.4</td>
<td>−2±0.7</td>
<td>0.0005*</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea</td>
<td>80±32</td>
<td>21±6</td>
<td>0.05*</td>
</tr>
<tr>
<td>Svr</td>
<td>82±22</td>
<td>21±6</td>
<td>0.008*</td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ees</td>
<td>70±16</td>
<td>7±12</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Data are mean±SEM; P values as reported by t test; *P<0.05.

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Exogenous NE resulted in a dose-dependent reduction in vessel diameter that was completely abolished by prazosin (maximum reduction in diameter; 33.4±4.3% versus 0.6±0.3%; WT versus WT+prazosin; n=4 to 7; P<0.001; Figure 2). In contrast to the EFS, there was no significant difference in the contractile response to 10 μmol/L NE in α1BAR KO mice versus WT (22.4±7.3% versus 33.4±4.3%; α1BAR KO versus WT; n=6 to 7; Figure 2). This suggests that the α1BAR plays a selective role in mediating contractile responses at the neuroeffector junction, whereas the other receptor subtypes (α1A or α1D) are likely important in mediating responses to exogenous catecholamines.

Discussion

The impaired pressor response to a hypotensive stimulus in the α1BAR KO mice, as well as the absent α1AR-mediated vascular contraction to endogenous NE release (EFS), strongly suggests that the α1BAR is critical in mediating sympathetic transmission at the neuroeffector junction. Furthermore, the preserved vascular contractile response to exogenous NE supports the role for other α1AR subtypes (α1A or α1D) in extrajunctional α1AR signaling. In addition, the α1BAR appears to be important in maintaining myocardial contractile function because mice deficient in the α1BAR have impaired endogenously stimulated adrenergically mediated contractile reserve and develop dilated LVs, as reflected by an increase in ventricular EDV.

Role of the α1BAR in Sympathetic Neuroeffector Signaling in Blood Vessels

There is significant heterogeneity in the expression of α1AR subtypes in vascular tissue. However, there is a paucity of data to indicate which receptor subtype mediates sympathetic neurotransmission at the synaptic neuroeffector junction. The notion of the existence of different α1AR subtypes in junctional versus extrajunctional neurovascular regions is supported by recent pharmacological studies in splenic arteries in vitro. Although periarterial EFS was inhibited by chloroethy-clonidine and LY-765 314 (α1AR specific antagonists), contractile responses to exogenous NE were preserved in an isolated canine splenic artery preparation. In contrast, WB4101, an α1AAR specific antagonist, inhibited exogenous NE-induced responses but had little effect on periarterial EFS-mediated vasoconstriction. The recent description of an α1BAR-specific circulating sympatholytic factor in a patient with orthostatic hypotension also supports the notion of a differential distribution of α1AR between junctional and extrajunctional regions. Preincubation of a porcine pulmonary artery (vascular ring bioassay) with sympatholytic dialyzed plasma attenuated the contractile response to exogenous phenylephrine but completely obliterated the response to periarterial EFS. Thus, our in vivo and in vitro vascular data support the concept that junctional receptors represent a different subtype to extrajunctional receptors and are most likely the α1BAR subtype. Evidence to support the role of α1BARs and α1AARs as extrajunctional receptors is provided indirectly by KO models. Specifically, the α1AAR and α1DAR KO mice demonstrated attenuated blood pressure responses to exogenous α1A agonists, and the α1DAR KO mice demonstrate impaired contractile responses in mesenteric vessels and aortic rings to exogenous NE. The clinical importance of this differential expression of adrenergic receptor subtypes is apparent in the selectivity displayed by certain α1AAR antagonists. For example, alfuzosin, a nonselective α1AAR antagonist, is associated with significant OI in males being treated for symptomatic benign prostatic hypertrophy. In contrast, tamsulosin, an α1AAR selective antagonist, is not associated with a greater incidence of OI than placebo. Thus, although the α1A and α1DAR may play a role in blood pressure regulation, the α1BAR is likely critical in mediating acute vascular responses to postural redistribution of blood volume.
α₁AR and Modulation of Myocardial Contractility and Structure

Although all α₁bAR subtypes are variably expressed in the heart, studies investigating their role in myocardial contractility and structure have yielded variable results that are species, age, and model dependent. The influence of α₁bAR on myocardial contractility has been assessed in overexpression and KO mutant models. α₁bAR overexpression impairs myocardial contractility via signaling pathways that include Gi coupling and cAMP and results in hypotension, autonomic failure, and cardiac hypertrophy.²² This apparent contrast with our results, which demonstrate impaired contractility in a KO model, could be attributable to indiscriminate activation of multiple signaling pathways by α₁bAR in the model overexpressing the receptor. Our results are more consistent with those of McClosky et al.,²³ who, in a murine papillary muscle preparation, demonstrated a contribution of α₁bAR and α₁aAR to a triphasic response provoked by α₁AR stimulation, including an initial increase in contractility with subsequent depression and recovery. Overall, the role of α₁bAR in modulating myocardial contractility in physiological conditions is likely to be modest and secondary to that of β-ARs. In contrast, in heart failure, α₁aARs are upregulated, whereas β-ARs are desensitized and downregulated. The potential importance of α₁AR was highlighted recently by the increased incidence of heart failure reported in patients administered nonselective α₁AR antagonists to treat hypertension and benign prostatic hypertrophy.²⁴ The role of α₁AR-specific subtypes in modulating contractility, specifically in pathophysiological conditions, remains to be investigated.
Data from cell culture and transgenic models indicate that α1aARs play an important role in modulating cardiac structure and involve the α1a, AR and α1b,AR subtypes with overexpression and deletion resulting in hypertrophy and atrophy, respectively, although 2 studies in a mouse model indicate that α1b,AR may not exert trophic changes in this species. However, our data indicating a dilated ventricle in α1b,AR KO mice support the premise that this specific adrenergic subtype may exert a trophic effect in mice.

Open-Loop Baroreceptor Function and Cardiovascular Response to Selective Carotid Baroreceptor Unloading

In addition to our findings related to the important role of the α1b,AR in cardiovascular regulation, we have applied the open-loop baroreceptor function technique to the mouse to interrogate baroreceptor-mediated control of the circulation. This technique has been useful for endogenous sympathoactivation in an attempt to address the hypothesis related to selective α1b,AR junctional signaling in vivo. This technique provides a unique way of stimulating the sympathetic nervous system by selective carotid baroreceptor unloading. It is invariable in assessing the efferent sympathetic response in this and other models of cardiovascular disease and promises to be as important in dissecting the contribution of signal transduction pathways in blood pressure regulation.

Limitations

It can be argued that the impaired responses to endogenous sympathoexcitation observed may be a function of impaired NE release in α1b,AR KO mice. Although we did not measure sympathetic nerve activity or NE spillover in this study, there is no evidence that there is a difference in monoamine content in brain tissue from WT versus KO mice. This suggests this is an unlikely mechanism to explain the results observed in vivo and in vitro. With regard to α1aARs, it is possible that dysregulation of these receptors in the α1b,AR KO mouse could explain the impaired responses to sympathoexcitation. Although there are postsynaptic α1AARs that mediate cold-induced vasoconstriction, visceral vascular α1AR are primarily presynaptic and negatively regulate the release of NE and transmitters from the sympathetic nerve terminal. Therefore, one would predict that pharmacological inhibition of α1aARs alone would enhance the vasoconstriction induced by EFS in WT vessels and would have little effect on vessels treated with prazosin or vessels from α1b,AR KO mice. We plan to address this issue in future experiments.

In summary, our data support the critical role of the α1b,AR as the receptor subtype mediating sympathetic neurotransmission at the neuroeffector junction. These data support the concept that junctional α1aARs are different from those that respond to circulating/exogenous NE. Together, our findings define a critical role for this receptor subtype in carotid arterial baroreceptor–stimulated sympathetic vasomotor tone, as well as maintenance of cardiac function and contractile reserve. This in turn has important implications for our understanding of the mechanisms associated with OI of dysautonomias, microgravity, and aging.

Acknowledgments

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