Vascular Function and Blood Pressure in GH Transgenic Mice

M. BOHLOOLY-Y, L. CARLSON, B. OLSSON, H. GUSTAFSSON, I. J. L. ANDERSSON, J. TÖRNELL, AND G. BERGSTRÖM

Institute of Physiology and Pharmacology, Department of Physiology, Göteborg University, Sweden; and Clinical and Experimental Research Laboratory, Lung and Heart Institute, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Acromegaly is associated with cardiovascular disease. We studied vascular function and mean arterial blood pressure in transgenic mice overexpressing bovine GH.

Mean arterial blood pressure was measured in conscious, unrestrained male and female bovine GH and littermate control mice during normal as well as high salt intake using telemetric devices. Structure in artificially perfused maximally dilated hindquarter vascular beds and vascular reactivity and endothelial function in small mesenteric vessels were studied in female bovine GH and control mice.

Mean arterial blood pressure was increased in female bovine GH transgenic (126 ± 3 mm Hg) and male bovine GH transgenic (129 ± 4 mm Hg) compared with female (109 ± 3 mm Hg, P < 0.05) and male (111 ± 3 mm Hg, P < 0.05) controls respectively. Increased salt intake had no effect on mean arterial blood pressure. Perfusion studies showed a significant decrease in the average diameter of the female bovine GH transgenic hindquarter vascular bed (P < 0.05). The responses of isolated resistance arteries to nor-epinephrine, potassium-induced depolarization, acetylcholine, or sodium-nitroprusside did not significantly differ between bovine GH transgenic and control mice.

We conclude that the phenotype of the bovine GH transgenic mice includes a salt-resistant form of hypertension. Furthermore, the increase in mean arterial blood pressure is accompanied by a significant structural narrowing of the resistance vasculature without changes in vascular reactivity or endothelial function. The results imply that hypertension in bovine GH transgenic mice is maintained mainly by a structurally based increase in peripheral vascular resistance. (Endocrinology 142: 3317–3323, 2001)

Human acromegaly is associated with development of hypertension, concentric left ventricular hypertrophy and ensuing cardiomyopathy (1, 2). Cardiovascular disease is the most common cause of death in the acromegalic patients (1). Presently it is not clear whether the high incidence of cardiovascular disease in acromegaly is a direct effect of GH or if the changes occur secondary to changes in mean arterial blood pressure (MAP).

Hypertension is reported in 20–40% of all acromegalic patients with a possible predominance in females (1, 2). The mechanisms behind the development of the high blood pressure are poorly understood. Administration of GH to healthy volunteers is in most studies not associated with hypertension (2). However, sodium retention and edema have been observed (3), possibly explained by a rise in plasma aldosterone and renin levels (4, 5). GH treatment in humans also results in an increase in heart rate and stroke volume (2). Because GH does not appear to affect blood pressure in humans, peripheral resistance has to be reduced. However, there is no real consensus in the literature, and a few studies report increased MAP after GH administration to humans (2).

In normotensive experimental animal models, GH administration (injections or GH-secreting tumors) has failed to affect MAP or vascular reactivity (6–9). However, cardiac hypertrophy has been observed, most likely of eccentric type with a large left ventricle and proportionally increased myocardium (10, 11). It has furthermore been shown that GH is needed for the development of high blood pressure and adaptive structural vascular changes in experimental renovascular hypertension (12).

Transgenic mice models, overexpressing GH, has been used in only a few studies of cardiovascular disease. Dilley and Schwartz (13) reported no difference in blood pressure but an increased media to lumen size in the mesenteric blood vessels of female transgenic C57/Bl6 mice overexpressing either rat GH or bovine GH (bGH). A recent study in a strain of C57Bl/6jcBA kept in our laboratory, overexpressing bGH, with elevated serum GH (1000–1400 ng/ml) and IGF-I (700–770 ng/ml) levels (14), showed that systolic cardiac function in these mice were compromised showing signs compatible with eccentric left ventricular hypertrophy (11). To further explore the cardiovascular function of this strain of GH transgenic mice, we used telemetric technique to measure 24-h blood pressure in conscious unrestrained animals. We also measured the blood pressure reaction to a diet enriched in sodium. Furthermore, we evaluated both structure and function of the resistance vasculature using wire myography technique and hindquarter perfusion of the mesenteric and skeletal vasculature, respectively.

Materials and Methods

Animals

Transgenes were generated using a metallothionein promoter (Mt) linked to a sequence encoding bGH using a BstEII-EcoRI fragment from...
the plasmid mtbGH2016 (generously donated by Dr. Palmiter, University of Washington, Seattle, WA). This construct was injected into pronuclear-stage C57Bl/6J×CBA embryos. Mice integrating the transgene were identified with PCR analysis of DNA from tail biopsy specimens obtained 3 wk after birth using one PCR primer located in the Mt promoter and another in the bGH gene.

Animals were housed together with littermate controls during most parts of the studies. However, during telemetric studies all mice were housed individually. The environment of the animal rooms was controlled with a 12-h light, 12-h dark cycle (0730 h, with a 1-h dawn/sunset function), a relative humidity between 45–55% and a temperature of 20°C. The mice had free access to tap water and standard pellet chow (R-34, Lactamin, Vadstena, Sweden). The study was performed after prior approval from the local ethical committee for animal experimentation at the Göteborg University, Sweden.

Groups of 5–7-month-old transgenic and littermate controls were randomly chosen for the different study protocols outlined below. However, in the studies using telemetry slightly younger mice were used (3–5 months of age). Only female mice were used for the studies of vascular function.

Blood pressure measurements

MAP and heart rate (HR) were continuously measured in freely moving bGH transgenic and littermate control mice of both sexes, using telemetry.

Surgical implantation of telemetry transmitters

Radiotelemetry transmitters were implanted in all animals at least 5 d before any experimentation. Mice were anaesthetized using medetomidine (Domitor, Orion Espoo, Finland, 0.055 mg/10 g, i.p.) and ketamine (0.75 mg/10 g, i.p). A telemetry transmitter catheter (OD 0.4 mm, Data Sciences International Inc., St. Paul, MN) was implanted into the carotid artery as previously described by Carlson (15). The transmitter (TA11PA-F20, weight 3 g) was positioned sc in the right flank of the animal and the incision closed with staples. Anaesthesia was reversed by atipamezole (Antisedan, Orion Espoo, 0.04 mg/10 g, p.o.). After at least 5–7 d of recovery, the cage with the animal was placed on a receiver plate and the signal collected using the Dataquest LabPRO Acquisition System (version 3.01, Data Sciences International, Inc.). The following sampling parameters were used; sampling frequency 300 Hz, sample duration 12 sec, save period 2 min. The pressure signal was corrected for electronic offset, the average of a measurement outside the animal before implantation and after exploitation.

Baseline telemetry MAP

Five to 7 d after implantation, MAP and HR were measured for 2 consecutive d in an undisturbed environment.

Effect of high salt

Effect of high salt diet was tested in female mice. After baseline recording of MAP and HR, the battery was turned off and the mice were administered a diet containing 8% NaCl (wt/wt, AnalyCen, Lidköping, Sweden) with free access to tap water. The mice were kept on this diet for 7 d, after which MAP and HR were recorded for another 2 d, still on high salt diet.

Renal function in conscious mice

Conscious renal function was measured in a sex-mixed group of bGH transgenic (n = 3) and matched wild-type control mice (n = 5). After anesthesia, a small mini-pump (ALZET, DURECT Corp., Cupertino, CA) was implanted sc, delivering a steady infusion of Cr-EDTA (Amersham International, UK) for 24 h (0.8 μCi/h). After 4 h recovery from anesthesia, the mice received a bolus injection of Cr-EDTA (5 μCi, i.p.) and were placed in separate metabolic cages for 24-h collection of urine. Blood samples were taken at the start and at the end of urine collection and the plasma was analyzed for radioactivity using a γ-counter (Packard 5019, Packard Co., Amana, IA). Glomerular filtration rate (GFR) was calculated by standard formulas (Urinary Cr-EDTA/Plasma Cr-EDTA × urinary-flow).

Hemodynamic studies of maximally dilated hindquarters

Female mice were prepared for hindquarter perfusions with a modified technique from that earlier described for rats (12). Briefly, the abdomen was opened and the aorta and vena cava cleared from tissue above the iliac bifurcation. The aorta was cannulated (PE-25) and perfusion of the hindquarter started with a 2% human albumin perfusate at 37°C (wt/wt, Immuno, Vienna, Austria). Temperature was maintained by an additional water jacket close to the aortic inlet and a heating lamp. The vena cava was cut wide open to minimize venous outflow resistance. The ionic composition of the perfusate was Na+ 148, K+ 4.9, Cl− 134, HCO3− 25, Mg2+ 0.83, Ca2+ 2.5, H2PO4− 0.6, and glucose 5.6 mmol. When bubbled with 5% CO2, the pH of the solution was 7.40. The perfusion was done alternating transgenic mice and their littermate controls. Baseline perfusion flow was set at 10 ml/100 g of hindquarter weight. The hindquarter was dissected out at the end of the experiment and weighed. The perfusion protocol consisted of random changes in the flow rate and simultaneous recordings of perfusion pressure in a t-tube close to the aortic inlet. Individual pressure-flow curves were established from which flow rates at designated pressures were estimated (10, 20, 30, 40, 50, 60, 70, and 80 mm Hg, see Fig. 4). We also tried to assess the maximal perfusor response by injecting a bolus-cocktail of angiotensin II, phenylephrine, and vasopressin V1 agonist in supraphysiological doses. However, due to technical problems with the low perfusion volumes and in-homogeneity of the responses, the data were impossible to interpret and are therefore not presented.

Mesenteric vascular function

Segments (approximately 2 mm long) of small arteries were taken from the mesenteric bed of female mice and mounted in a MultiMyograph 610M (Danish Myo Technology, Aarhus, Denmark) for recordings of their isometric wall tension at well-defined internal circuminferences. Normalized internal diameters were 221 ± 16 and 213 ± 33 μm for control and bGH, respectively (16). Solutions were equilibrated with 5% CO2 (pH 7.4), and bath temperature was maintained at 37°C. The composition (in mM) of the physiological salt solution was NaCl 119, NaHCO3 25, glucose 5.5, KCl 4.7, CaCl2 2.5, KH2PO4 1.18, MgSO4 1.17, EDTA 0.026. Cumulative concentration-response relationships were obtained by applying nor-epinephrine (NE, range 0.008–10 μmol) increasing the concentration 2-fold every 2 min. Cumulative concentration-response relationships of KCl were obtained by applying salt solution where part of the NaCl were replaced by equimolar amount of KCl (range 15–125 mm), increasing the concentration by 1.5 every 2 min. The function of the endothelium was evaluated by the response to acetylcholine (Ach) and compared with the response to the endothelium-independent vasodilator sodium-nitroprusside (SNP). Ach (range 10−7–10−5 mol) and SNP (range 10−11–10−8 mol) were administered in a cumulative way, on precontracted vessels (NE, maximal contraction), increasing the concentrations in half log steps every 4 min. A second dose-response relationship to Ach was performed in the presence of the nitric oxide (NO)-synthase inhibitor Nω-nitro-L-arginine (L-NNA, 100 μmol).

Statistics

Body-, heart-weights, and MAP before and after salt were compared using t test. MAP from telemetry was compared using an ANOVA followed by the Dunnett post hoc testing for differences from control. Hind-quarter vascular resistance was compared using a repeated measured ANOVA. Concentration-response relations in the Myo-graph were analyzed with nonlinear regression (GraphPad Systems) giving Emax as the maximal response and EC50 as the concentration giving half-maximal response. Statistical analysis was performed by means of t test for paired or unpaired observations. Probability level of less than 0.05 is regarded as significant. Values are given as means ± SEM.
Results

Heart and body weights

As previously reported (11), body weight was increased by 37% in bGH transgenic mice, and left ventricular weights per body weight were increased by 49% in the female transgenic mice compared with wild-type control mice (Table 1). The increase in left ventricular weight was in excess of the increase in body weight and also well in excess of the observed increase in blood pressure (17%).

Blood pressure

Using telemetric technique, we could show that bGH transgenic mice irrespective of gender had a significantly higher MAP (Fig. 1, \( P < 0.01 \) for both). When female mice were fed a diet enriched in sodium for 1 wk to test for salt sensitive hypertension, neither bGH transgenic nor female control mice responded with any significant change in MAP (Table 2). However, HR was significantly decreased in both bGH transgenic and female littermate control mice (\( P < 0.05 \), Table 2).

Renal function in conscious mice

GFR was significantly higher in a sex-mixed group of bGH transgenic mice compared with sex-mixed control mice (bGH = 410 ± 17, control = 230 ± 36 \( \mu \)l/min, \( P < 0.05 \)). However, no significant difference could be detected when GFR was related to body weight (bGH = 6.3 ± 0.3 \( \mu \)l/min-g body weight, control = 5.2 ± 0.9 \( \mu \)l/min-g body weight, NS).

Hemodynamic studies of maximally dilated hindquarters

Perfusion of the hindquarter at maximal dilatation revealed that female bGH transgenic mice needed a higher flow to reach the same perfusion pressure as the littermate control, i.e. a higher resistance in the bGH transgenic mice hindquarter (Fig. 2). The higher resistance in the bGH transgenic hindquarter is equivalent to a narrower average lumen diameter in this vascular bed, compared with littermate control mice (law of Poisuelle’s).

Mesenteric vascular function

Small vessels taken from the mesenteric vascular bed of female bGH transgenic responded with similar development of tension as did littermate control mice to both the adrenergic agonist NE and the unspecific depolarization by hyperkalemia (Fig. 3). However, the sensitivity of the response to NE was significantly shifted to the right in the bGH transgenic mice (\( EC_{50} \), \( P < 0.05 \)), suggesting a decreased sensitivity of the bGH transgenic mice vascular bed to the vasocostrctor action of NE (Fig. 3).

The vasodilator response to Ach was similar in both the female bGH transgenic and the littermate control mice (Fig. 4). Pretreatment with l-NNA resulted in a reduction but not a complete abolishment of the vasodilator action, suggesting that the action of Ach is mediated both by release of NO as well as endothelial hyperpolarizing factor (EDHF). SNP resulted in similar vasodilator response in both female bGH transgenic and littermate control mice (Fig. 4).

Discussion

The major finding in the present study was that hypertension was present in both male and female transgenic mice overexpressing the gene for bGH. This finding suggests that the bGH transgenic mice is a suitable animal model for studies of cardiovascular disorders in acromegaly. Furthermore, we found a reduction in the average lumen dimensions at maximal dilatation in the skeleton muscle bed (hindquarter). However, we found no change in endothelial function or maximal vascular constrictor capacity of isolated vessel segments from the mesenteric vascular bed. Furthermore, the MAP of the bGH transgenic mice were not affected by salt loading suggesting a salt-resistant form of hypertension.

Blood pressure

We have shown that MAP was increased in female and male bGH transgenic compared with littermate control mice. Human acromegaly is associated with an increased prevalence of hypertension (20–40%); however, results from animal studies are more controversial. When using different injection techniques of GH or surgical implantation of GH-producing tumors, the effect on MAP is not consistent between studies (2), although most studies showing no effect of GH on MAP.

The information on blood pressure levels of GH-transgenic mice is limited. Dilley and Schwartz (13) reported no increase in the systolic blood pressure of female GH-transgenic mice. Noteworthy is that they found systolic blood pressure, measured with tail-artery plethysmography, to be in the range of 90–95 mm Hg. This is remarkable low because the SBP recorded by telemetry in the control normotensive mice in our study was in the range of 130–150 mm Hg. Indeed, several studies have shown MAP of mouse to be in the same range as in other rodents. The low MAP in the study by Dilley (13) points to important methodological differences between our studies making comparisons difficult.

In the present study, we used sophisticated, state-of-the art telemetry equipment to measure blood pressure. MAP was increased to the same extent in both sexes of bGH transgenic mice. Telemetric measurement of blood pressure in mice is a new technique (15) but must nevertheless be con-

### Table 1. Body and heart weight as well as 24-h mean arterial blood pressure in female bGH transgenic and littermate control mice

<table>
<thead>
<tr>
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<th>Control (n = 7)</th>
<th>Transgenic (n = 7)</th>
<th>% difference</th>
<th>P value</th>
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<tr>
<td>MAP (mm Hg)</td>
<td>109 ± 3</td>
<td>126 ± 3</td>
<td>17%</td>
<td>&lt;0.01</td>
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<td>Body weight (g)</td>
<td>44 ± 2</td>
<td>61 ± 3</td>
<td>37%</td>
<td>&lt;0.01</td>
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<td>Left ventricular weight (µg/10 g BW)</td>
<td>207 ± 7</td>
<td>309 ± 17</td>
<td>49%</td>
<td>&lt;0.001</td>
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<td>Right ventricular weight (µg/10 g BW)</td>
<td>68 ± 6</td>
<td>83 ± 5</td>
<td>22%</td>
<td>&lt;0.001</td>
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considered as the gold standard for MAP measurements. In a unique way, the technique allows us to measure the true, unrestrained MAP of mice in their normal environment. From the data in the present study, we conclude that both sexes of bGH transgenic mice of the studied strain are hypertensive.

Acute administration of human GH leads to salt and water retention (3). Furthermore, previous reports have shown a higher incidence of glomerulosclerosis in old bGH transgenic mice (17). Thus, it could be speculated that an impaired excretory capacity or a volume retaining action of GH could explain the high MAP. We therefore analyzed renal function in a subgroup of conscious male and female bGH transgenic mice. GFR in the bGH transgenic mice were unchanged, arguing against excretory failure as an explanation to the high MAP. Furthermore, MAP in the bGH transgenic mice were not affected by an approximately 10-fold increase of salt ingestion (8% in food); therefore, it is unlikely that the observed hypertension is salt dependent.

**TABLE 2.** MAP and HR in female bGH and littermate control before and after 7 days of high salt food

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Data are the average value from 48 h recording before and day 8 and 9 after the start of salt loading. NS, Not significant; *P < 0.05; **P < 0.001 difference compared with normal salt.

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**FIG. 1.** MAP and HR measured with telemetry in female (n = 7) and male (n = 4) mice, transgenic for bGH. Littermate female (n = 7) and male (n = 4) mice served as control. *P < 0.01 denotes outcome of ANOVA analyzing the average MAP and HR over 24 h compared with littermate control.

**FIG. 2.** Pressure-flow curves derived from artificially perfused maximally dilated hindquarters of female bGH transgenes (▲, n = 5) as well as littermate controls (n = 4).

**Vascular function studies**

What might be the mechanisms behind the increased MAP in bGH transgenic mice? In an attempt to answer this question, we analyzed vascular structure and function in both the hindquarter vascular bed (skeletal muscle) and in isolated vessels from the mesenteric bed of female mice. The techniques complement each other and give important insights in to the pathophysiology of bGH hypertension.
Hindquarter vascular resistance

The hemodynamic technique to study resistance in the maximally dilated skeletal vascular bed of the hindquarter has been used extensively in rats to deduce the structure of the vasculature (18). With this technique, it has been established that the hallmark of all forms of hypertension is an increased resistance of the vascular bed at maximal dilatation (18, 19). This corresponds to a decrease in the average lumen dimensions of the vascular bed, which will have severe implications for blood pressure control as reviewed previously (19). In the present study, we found resistance to be increased, and thus we interpret this as a decrease in the average lumen dimensions of the hindquarter. However, it is important to note that this finding could both cause and be the result of the increased pressure (18), and it is thus difficult to draw any firm conclusions on the pathogenetic importance of these findings. The finding is in apparent contrast to the finding by Dilley and Schwarz (13) that the average lumen diameter was increased in several vascular sections. However, it is important to note that the whole organ perfusion technique used in the present study is averaging the lumen diameters along the whole length of the vessel. The morphological technique used by Dilley only gives a spot measurement at one defined level of the vasculature. Furthermore, the vessels in the study by Dilley (13) were fixed at the assumed physiological pressure and not at maximal dilatation allowing for sampling artifacts. The effect of GH injections on vascular structural properties in hindquarters has previously been studied in rats subjected to hypertension due to experimental renal artery stenosis (12). This study pointed to a permissive role for GH in the structural adjustment of the vasculature to an increased pressure load. Furthermore, GH administration to hypophysec-tomized rats resulted in encroachment of the vascular lumen in the hindquarter thus confirming our results. It is thus possible that excess GH could be of primary pathophysiological importance in the development of hypertension in GH transgenic mice by remodeling the resistance vasculature.

Mesenteric vascular function

We also studied vascular function and reactivity in isolated segments of the mesenteric bed. Using this technique, we can estimate the reactivity of the vascular bed to different agonists. In the present study, we evoked vascular constriction both by the adrenergic agonist, NE, and the unspecific, depolarizing effect of hyperkalemia. We found no difference in the maximal constriction evoked by these two substances between the bGH transgenic and the littermate control mice. However, the sensitivity to applied NE was significantly reduced in the bGH transgenic mice, with a rightward shift of the dose-response curve. This implies down-regulation of NE-receptors or second messenger systems but with an intact maximal contractile strength of the vessel. One explanation for this finding could be a down-regulation of adrenergic receptors secondary to an increased sympathetic drive. It is interesting to speculate that hypertension in bGH transgenic mice is caused by, or associated with, an increase in sympathetic drive, which results in a decreased NE sensitivity in the vasculature (see below). This hypothesis remains to be tested.
As discussed above, vascular reactivity is dependent on both the function of the smooth muscle cells and the geometry of the vessels, i.e., vessel-wall size in relation to lumen dimensions (18, 19). Thus, to be able to fully describe the function of the vasculature in the bGH transgenic mice, we would also need reliable data on wall-size in the vessels studied. Detailed future analyses of both the contractile properties of the bGH transgenics smooth muscle cells and a proper analysis of wall size in relation to lumen dimension could shed further light on the pathogenesis of the hypertension in bGH transgenic mice.

Human acromegaly is associated with both hypertension (20–40%) and diabetes (10–20%) (1). Both these disorders have been associated with endothelial dysfunction (20, 21) and could thus be an important pathogenetic component in development of bGH transgenic mice hypertension. Despite the very high serum levels of GH found in the bGH transgenic mice (14), blood glucose levels are similar in bGH transgenic and littermate control mice (22). However, even though no regular insulin sensitivity test has been performed, the insulin levels has been shown to be markedly higher in bGH transgenic mice compared with controls, suggesting a marked insulin resistance in these mice that could affect endothelial function (22). The myo-graph technique allows us to test the endothelial function of the vessel. Administration of Ach triggers release of two endothelium-dependent vasodilators: NO and EDHF (23). However, the similar results between the two experimental groups suggest that endothelial function is intact in the bGH transgenic mice.

The vascular dilatation was substantially, but not totally, inhibited by a blocker of NO formation (L-NNA). This finding implies that most of the Ach-induced vascular dilatation was caused by NO release with a small contribution from EDHF. The administration of the direct NO donor, sodium nitroprusside, shows that the reactivity to NO is similar in bGH transgenic and littermate controls mice. Thus, we can conclude that endothelial dysfunction is not a major pathogenetic factor in bGH transgenic mice hypertension.

**Integrative control of blood pressure in bGH transgenes**

Our current data showing that an increased salt ingestion does not result in an increase in MAP argues against a salt-sensitive form of hypertension. In an earlier study using the same strain of bGH transgenic, it was clear that despite cardiac hypertrophy in excess of body weight increase (Table 1), the systolic cardiac function were markedly compromised, showing signs compatible with eccentric left ventricular hypertrophy (11). Even though we cannot estimate cardiac output from these studies, it is hard to reconcile the impaired systolic function with an increase in MAP. However, together with the results in the present study showing vascular narrowing of the hindquarter vascular bed and a normal contractile strength of the mesenteric vasculature, it is likely that the MAP in bGH transgenic mice is maintained by an increase in peripheral vascular resistance based mainly on vascular...
narrowing of the resistance vasculature. Furthermore, it has been proposed that insulin can stimulate the activity of the sympathetic nervous system and cause vasoconstriction and hypertension (24). Thus, the high insulin levels observed in the bGH transgenic mice (22) could stimulate the sympathetic nervous system and be important pathogenetic factors contributing to the increase in peripheral resistance and hypertension of the bGH transgenic mice. Supporting the notion of an increase in sympathetic tone is the observed decrease in NE sensitivity in the small mesenteric vessels.

Conclusion

We have shown, using telemetric technique, that mice overexpressing bGH irrespective of gender have an increased MAP that is not salt sensitive. This increase in MAP is associated with a narrowed lumen of the hindquarter vasculature. However, there was no difference in the contractile strength of the mesenteric vascular wall, nor any difference in endothelial function between bGH transgenic and littermate control mice. The finding of a hypertensive phenotype suggests that the bGH transgenic mice is a valid model for studies of cardiovascular disease in human acromegaly. This implies that the hypertension in bGH transgenic mice is mainly maintained by a structurally based increase in peripheral vascular resistance, perhaps augmented by the sympathetic stimulatory effect of hyperinsulinemia.

Acknowledgments

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Address all correspondence and requests for reprints to: Göran Bergström, Institute of Physiology and Pharmacology, Department of Physiology, P.O. Box 432, 405 30 Göteborg, Sweden.

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