Vascular Remodeling in the Growth Hormone Transgenic Mouse

Rodney J. Dilley and Stephen M. Schwartz

Using mice transgenic for the growth hormone gene (TGHM), we have studied the effects of a systemic elevation of growth hormone on vascular growth with the aim of investigating the role of vascular mass changes in producing hypertension. In contrast to human acromegaly or gigantism, there was no elevation of blood pressure in TGHM, but there were significant increases in vascular wall mass. In accordance with a presumably increased perfusion of larger organs, the medial cross-sectional areas of thoracic aorta and mesenteric resistance vessels were greater in the TGHM. These differences could be normalized in the aorta by body weight and in the mesenteric vessel by small intestine weight. Furthermore, the brain was not significantly heavier in the TGHM, and their carotid and cerebral vessels also were not larger. Wall-to-lumen ratios were similar in the aorta, carotid, and middle cerebral arteries suggesting that wall stress was the controlling factor in wall thickness. Surprisingly, the mesenteric vessels had increased wall-to-lumen ratio, which was similar to that seen in hypertensive vascular remodeling but in a normotensive animal. In an attempt to explain this finding it was noted that the pattern of mesenteric vascular networks and even organized structure within the vessel wall itself appeared to be fixed, perhaps by genetic mechanisms. Thus, vascular network structure may be a potentially limiting factor in the ability of the vessel wall to remodel and may have been responsible for the greater wall-to-lumen ratio in TGHM mesenteric vessels. A similar situation in human acromegaly or gigantism could result in a circulation marginally able to correct for other demands on blood flow resulting in about one third of cases being hypertensive.

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The status of the blood vessel wall in animals with growth hormone excess is of interest because of the high incidence of hypertension in acromegaly and gigantism. Despite the many endocrine modulations caused by excess growth hormones, there is no apparent endocrine explanation for the increased blood pressure in these individuals.2,3

We have studied mice transgenic for the growth hormone gene (TGHM) as a possible model for these human disorders. Of interest to us has been the hypothesis that the increase in blood pressure in humans with excess growth hormone might be a direct result of increased mass of the wall of resistance vessels. This would be consistent with a hypothesis offered by Folkow.4 Using a combination of physiological and morphometric techniques, Folkow and others have demonstrated that the increase in peripheral resistance in hypertension, irrespective of the primary etiology of the disease, can in most cases be accounted for by an increased mass of the hypertensive vessel wall. While the decrease in lumen size may be relatively small in a relaxed vessel, increased vascular wall mass greatly amplifies the extent of contraction resulting from vasoactive stimuli and, thus, markedly increases resistance to blood flow and systemic blood pressure. In further support of our hypothesis, Ledet5 found that growth hormone added to primary cultures of vascular smooth muscle cells stimulated growth of those cells. Thus, elevated growth hormone in vivo may increase resistance via smooth muscle mass and produce an increase in blood pressure. It would be of interest to know whether a primary increase in growth hormone production alters vessel wall structure and also whether the alteration of vessel wall structure is associated with an elevation in blood pressure.

Materials and Methods

Female (C57) mice expressing the MT-rGH or MT-bGH gene construct,6,7 along with nontransgenic littermates for controls, were obtained at 4
weeks of age. Body weights and blood pressures were measured from the second to the seventh month of age in these animals.

Blood pressures were measured in conscious animals by tail-cuff occlusion techniques with a plethysmograph (Narco Biosystems, Houston, Texas). After prewarming in a restrainer for 4–5 minutes, at least three measurements were taken on each animal over several minutes, and the average was recorded as the blood pressure for that session.

At 7 months of age, six control and six MT-rGH transgenic animals were perfused at 90 mm Hg pressure via the abdominal aorta with Ringer's lactate for 3 minutes, followed by fixative solution (2% glutaraldehyde plus 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4) at the same pressure for 10 minutes.8

The heart, thoracic aorta, left common carotid artery, brain, left kidney, and adrenal gland were removed and placed in fixative overnight. Approximately 20 cm of distal small intestine (jejunum and ileum) and its attached mesentery were also removed and placed in fixative. The heart, brain, kidney, and adrenal gland were blotted dry and weighed. In the mesentery the following two types of vessels were counted: arteries that penetrated the wall of the gut (first-order branches) and two levels of arteries proximal to the wall (third-order branches). Four of the third-order branches (large muscular arteries, 50–100 μm diameter) were selected from the distal end of the intestine for light microscopy. Four blocks of carotid artery and four blocks of aorta were also selected. One block containing left middle cerebral artery and carotid artery, brain, left kidney, and adrenal gland were blotted dry and weighed. In the mesentery the following two types of vessels were counted: arteries that penetrated the wall of the gut (first-order branches) and two levels of arteries proximal to the wall (third-order branches). Four of the third-order branches (large muscular arteries, 50–100 μm diameter) were selected from the distal end of the intestine for light microscopy. Four blocks of carotid artery and four blocks of aorta were also selected. One block containing left middle cerebral artery and underlying brain tissue was also taken. All tissues were rinsed in buffer and processed for light microscopy.

Sections of aorta, common carotid artery, middle cerebral artery, and small mesenteric arteries were analyzed on an Olympus microscope fitted with a camera lucida that projected the image directly over a graphics tablet. The inner and outer elastic laminae were traced directly onto the graphics tablet, and areas of the lumen and media were calculated and placed in fixative. The heart, brain, kidney, and adrenal gland were blotted dry and weighed. In the mesentery the following two types of vessels were counted: arteries that penetrated the wall of the gut (first-order branches) and two levels of arteries proximal to the wall (third-order branches). Four of the third-order branches (large muscular arteries, 50–100 μm diameter) were selected from the distal end of the intestine for light microscopy. Four blocks of carotid artery and four blocks of aorta were also selected. One block containing left middle cerebral artery and underlying brain tissue was also taken. All tissues were rinsed in buffer and processed for light microscopy.

DNA Content and Ploidy Analysis

The entire aorta was dissected, the length and weight of the vessel were measured, and a 1-cm portion distal to the third intercostal artery was removed and stored at −70° C for subsequent DNA analysis. For flow cytometry the thoracic aorta was stripped of adventitia and endothelium, and smooth muscle cells were dispersed in a collagenase plus elastase solution at 37° C. The resulting cell suspension was filtered through a 70-μm steel mesh to remove tissue debris and centrifuged at 1,500 rpm for 8 minutes. The supernatant was discarded and cells were resuspended in nuclear isolation medium containing Tris-buffered isotonic saline (pH 7.0), 0.6% Nonidet P-40, 21 mM MgCl2, and 10 μg/ml 4,6-diamidino-2-phenylindole, for flow cytometry on an ICP-22 flow cytometer (Ortho Diagnostic Systems, Raritan, New Jersey). Determination of the proportion of the cell population in the G2 peak was by the method of Dean and Jett.9 Nonlinear least-squares fitting was by the method of Marquadt.10

The DNA content of thoracic aorta was measured by the fluorescent assay of Labarca and Paigen,12 but a lithium chloride buffer (2 M LiCl and 50 mM Tris, pH 7.5) was used throughout. After stripping the adventitia and intima, the media was weighed and its length was measured. It was then ground in a glass homogenizer, sonicated, and centrifuged at 10,000g for 20 minutes to remove debris from the suspension. The supernatant was used to estimate DNA content per unit length of vessel by the fluorescence of Hoechst 33258 dye in a TKO 100 miniflowmeter (Hoefer Scientific Instruments, San Francisco, California). DNA standards were made from purified calf thymus DNA (Pharmacia, Piscataway, New Jersey). Mean values were compared by t test. A level of p < 0.05 was considered significant.

Results

Body and Organ Weight

Mean body weights were different at 4 weeks of age, and the ratio of mean body weights (transgenic/control) increased from 1.4 to over 1.7 within 2 months and was maintained at this level up to 7 months. The organs sampled at 7 months generally reflected this increased body weight, including the kidney, heart, small intestine, and adrenal gland (Table 1). The brain was not significantly increased in weight; thus, lower brain/body weight ratios in TGHM resulted. The aorta of TGHM

S=(P · r)/t

where P was the average of tail-cuff blood pressures measured on the last 3 days before sacrifice. Statistical analysis of cross-sectional area data was by ANOVA because of subsampling in this hierarchical design.9 Other parameters were compared by t test.
TABLE 1. Characteristics of 7-Month-Old Mice Transgenic for the Growth Hormone Gene and Littermate Control Mice

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Transgenic</th>
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</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>88.0±3.7</td>
<td>88.3±3.7</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>27.4±0.9</td>
<td>46.9±1.7*</td>
</tr>
<tr>
<td>Heart weight (mg)</td>
<td>137±8</td>
<td>242±16*</td>
</tr>
<tr>
<td>Kidney (mg)</td>
<td>189±9</td>
<td>369±38*</td>
</tr>
<tr>
<td>Adrenal (mg)</td>
<td>3.3±0.3</td>
<td>5.0±0.4*</td>
</tr>
<tr>
<td>Brain (g)</td>
<td>0.50±0.01</td>
<td>0.51±0.03</td>
</tr>
<tr>
<td>Heart wt/body wt (10^-3)</td>
<td>5.1±0.4</td>
<td>5.4±0.3</td>
</tr>
<tr>
<td>Kidney wt/body wt (10^-3)</td>
<td>7.0±0.4</td>
<td>8.1±0.5</td>
</tr>
<tr>
<td>Adrenal wt/body wt (10^-3)</td>
<td>0.12±0.01</td>
<td>0.11±0.01</td>
</tr>
<tr>
<td>Brain wt/body wt (10^-3)</td>
<td>18±1</td>
<td>11±1*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *p<0.05 vs. control values.

was not significantly longer than controls (mean length±SEM: TGHM, 3.87±0.10 cm; control, 3.07±0.20 cm) but was heavier (TGHM, 0.0094±0.0007 g; control, 0.0044±0.0006 g).

Blood Pressure

Tail-cuff pressures obtained from 14 TGHM were not significantly different from 14 control littersmates (tail-cuff pressure±SEM: TGHM, 97.5±3.9 mm Hg; control, 95.8±3.2 mm Hg). The blood pressures of the six TGHM and six control animals that were used for morphometric studies were also not significantly different (transgenic, 88.3±3.2 mm Hg; control, 88.0±3.7 mm Hg).

The TGHM animals appeared to be more sensitive to the training effect; this sensitivity was apparent when measuring blood pressures by the tail-cuff procedure.13 When first measured, the pressures in TGHM were slightly higher but normalized over time. We have no way of assessing possible elevation of blood pressure when animals were not being handled.

Vessel Wall Mass

The histological appearance of the arterial wall was similar in TGHM and control mice (Figure 1), but the cross-sectional area of the thoracic aorta media was greater in TGHM (Figure 2). The number of medial lamellae (i.e., layers of elastin and smooth muscle) was the same in TGHM and control mice (Table 2), so the extra mass must be distributed as thicker layers, rather than more layers. When normalized to body weight, the medial area was not different (Figure 3). Aortic wall-to-lumen ratios (Figure 4) and the calculated values for wall

![Figure 1. Photomicrographs of histological sections of control (panel a) and transgenic (panel b) mouse thoracic aorta at 7 months of age. The vessels were histologically similar, and the same number of medial lamellae were evident (Richardson's stain). Bar, 30 μm.](http://circres.ahajournals.org/)

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FIGURE 2. Bar graphs showing medial cross-sectional area of thoracic aorta, common carotid artery, and third branching order mesenteric resistance arteries. The thoracic aorta and mesenteric vessel areas were significantly different, but the carotid vessel areas were not.

stress (Table 2) also were not significantly different.

The mean DNA content per unit length of abdominal aorta in the TGHM was greater than control values (Table 3). These differences did not parallel body weight changes, and when corrected for body weight, the control values were actually greater than the TGHM values. The aortic DNA content more closely followed aortic weight, and the DNA content per aortic weight was not significantly different in TGHM and control animals.

Flow cytometric analysis of the proportion of cells with tetraploid or higher DNA content revealed a degree of smooth muscle cell polyploidization in TGHM thoracic aorta that was not different from control aorta (Table 3). These data, together with the mean DNA content from similar animals, show a 30.8% increase in cell number in the thoracic aorta of TGHM.

The carotid artery medial cross-sectional areas did not differ between TGHM and control mice (Figure 2), nor was there a significant difference between weight of the brain or head (Table 1). The value obtained by dividing the TGHM carotid medial area by body weight was somewhat lower than expected. If brain weights were used instead of body weights, the TGHM carotid vessel mass was maintained at the same level as control mice (Figure 5).

The conclusion from these results is that TGHM have greater arterial medial mass when the end organ mass is greater, as in the mesenteric vessels and aorta, but not in the brain, where organ mass was the same in TGHM and controls.

Two animals in the TGHM group had middle cerebral artery medial areas over 50% greater than the control group mean. The p value for the TGHM group as a whole, however, was not significant at the 0.05 level (TGHM, 2.81±0.33 mm²×10⁻³; control, 1.96±0.21 mm²×10⁻³; p=0.056). The wall-to-lumen ratios also were variable, and in TGHM middle cerebral arteries were not different from controls (TGHM, 0.170±0.038; control, 0.116±0.008).

Vessels of the TGHM ileal mesentery had a greater medial cross-sectional area (Figure 2, Table 4), and in these vessels the wall-to-lumen ratio was greater in the TGHM than in controls (Figure 4). Lumen areas did not increase to the same extent as wall areas (Table 4). Interestingly, the cross-sectional area of the vessel media per unit gut weight was constant (Figure 5).

Table 2. Medial Lamellae, Medial Thickness, Lumen Radius, Wall Tension, and Stress in Transgenic and Control Aorta Values

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Transgenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial lamellae</td>
<td>5.1±0.1</td>
<td>5.0±0.1</td>
</tr>
<tr>
<td>Medial thickness (µm)</td>
<td>29±2</td>
<td>36±2*</td>
</tr>
<tr>
<td>Vessel radius (mm)</td>
<td>0.41±0.02</td>
<td>0.47±0.03</td>
</tr>
<tr>
<td>Tension (dynes/cm×10⁹)</td>
<td>4.81±0.39</td>
<td>5.58±0.43</td>
</tr>
<tr>
<td>Wall stress (dynes/cm²)</td>
<td>1.76±0.25</td>
<td>1.61±0.16</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.05 vs. control values.
TABLE 3. DNA Content and Polyploidy in Thoracic Aorta of Transgenic and Control Mice

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Transgenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial DNA content (ug/cm)</td>
<td>2.87±0.16</td>
<td>3.91±0.12*</td>
</tr>
<tr>
<td>DNA/body wt (10^-3/g)</td>
<td>0.122±0.007</td>
<td>0.078±0.003*</td>
</tr>
<tr>
<td>Aorta wt/body wt (10^-3)</td>
<td>54.7±3.9</td>
<td>39.9±1.1*</td>
</tr>
<tr>
<td>DNA/aorta wt (10^-3/g)</td>
<td>2.29±0.17</td>
<td>1.96±0.08</td>
</tr>
<tr>
<td>Polyploid cells (%)</td>
<td>4.2±1.1</td>
<td>6.4±1.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *p<0.05 vs. control values.

Vascular Density

Frequency of branching and total numbers of branches at two different levels of the mesenteric network were expressed in relation to the weight and length of tissue supplied (Table 4). In the first set of animals examined, the branching patterns (the ratio of third-order to first-order branches) of mesenteric vessels supplying the distal 20 cm of small intestine were constant. However, when corrected for gut weight or gut length supplied, the number of vessels was lower in TGHM. In a second set of animals, the entire length of the small intestine was removed, weighed, and measured. These results show that TGHM have a significantly longer (TGHM, 21.4±0.5; control, 21.4±0.8) branch vessels (TGHM, 21.4±0.5; control, 21.4±0.8) and first-order branch vessels (TGHM, 172±5; control, 166±6) was constant and, therefore, independent of gut size. Thus, growth hormone had an effect on the size of an individual vessel’s perfusion field and on its wall mass, but vascular network structure was unaffected by growth hormone or by secondary effects mediated through end-organ mass.

Discussion

Approximately one third of patients with a congenital or acquired excess of growth hormone dem-

FIGURE 5. Bar graphs showing medial area of the carotid and mesenteric vessels corrected for their end-organ weight (brain and gut, respectively). Values for mice transgenic for the growth hormone gene were not significantly different from controls.

onstrate hypertension. Attempts to identify a humoral mechanism able to account for the elevated pressure have not succeeded. Therefore, we were intrigued to consider the possibility that the elevation of blood pressure in growth hormone excess might be due to a primary effect of growth hormone, or some other endocrine factor affected by growth hormone, on smooth muscle mass. As proposed by Folkow, an increase in mass would create an increased response to vasoactive stimuli, which would effectively increase peripheral resistance. Unfortunately for this hypothesis, we would interpret the data presented here as negative because: 1) systemic elevation of growth hormone did not have a direct effect on vascular mass and 2) there were increases in wall mass but not in blood pressure. Instead, we suggest that growth hormone alters distal perfusion demands by changing local rheological conditions and by secondarily stimulating vascular remodeling.

A critical part of our interpretation of these data is the observation that not all organs or vessels were affected in the same way by growth hormone excess. For example, wall area and wall-to-lumen ratio in the carotid and cerebral arteries were the same in TGHM and control animals. These vessels conduct blood to a region of the body where mass was not affected by the presence of the transgene to excess growth hormone levels. In contrast, the aorta supplied blood to a larger body mass in TGHM. The area of the thoracic aorta was 40% greater in TGHM than in control mice. A simple explanation of these data may arise from studies by Gothberg and Folkow of trophic responses in the renal artery feeding a hypertrophic kidney. These investigators found an increase in wall radius and wall thickness presumably representing an adaptation to increased demands for blood flow. We propose that, as mass of the body or individual organs increases in TGHM, the perfusion demand is cor-

TABLE 4. Small Intestine and Mesenteric Vascular Changes in Mice Transgenic for the Growth Hormone Gene and Control Mice

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Transgenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut wt/length (mg/cm)</td>
<td>5.82±0.51</td>
<td>7.95±0.60*</td>
</tr>
<tr>
<td>Vessel density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First order/gut wt (mg)</td>
<td>95.7±6.8</td>
<td>58.9±5.1*</td>
</tr>
<tr>
<td>Third order/gut wt (mg)</td>
<td>10.0±0.7</td>
<td>6.2±0.3*</td>
</tr>
<tr>
<td>First order/cm gut</td>
<td>5.08±0.14</td>
<td>4.29±0.07*</td>
</tr>
<tr>
<td>Third order/cm gut</td>
<td>0.49±0.02</td>
<td>0.40±0.01*</td>
</tr>
<tr>
<td>First order/third order</td>
<td>10.8±0.6</td>
<td>10.6±1.0</td>
</tr>
<tr>
<td>Third-order branches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial area (mm² x 10^-3)</td>
<td>2.80±0.44</td>
<td>4.03±0.42*</td>
</tr>
<tr>
<td>Area/body wt (mm² x 10^-3/g)</td>
<td>1.02±0.22</td>
<td>0.89±0.16</td>
</tr>
<tr>
<td>Area/gut wt (mm² x 10^-3)</td>
<td>24.0±2.4</td>
<td>27.2±3.1</td>
</tr>
<tr>
<td>Lumen area (mm² x 10^-3)</td>
<td>15.3±6.2</td>
<td>17.6±3.3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *p<0.05 vs. control values.
The TGHM aorta, like a hypertensive aorta in the rat, shows an increase in DNA content. In hypertensive rats, this increase, which may occur by polyploidy rather than by increased cell number, results in a DNA content sufficient to maintain a roughly constant DNA/mass ratio. Similarly, the TGHM shows a parallel increase in DNA content and total mass. However, there is no change in ploidy. Hyperplastic rather than hyperploid changes have also been described in the resistance arteries of the hypertensive rats and in the aorta responding to coarctation hypertension, but again the DNA content is appropriate for vessel wall mass in these models. Based on the similar increase in DNA content in nonhypertensive TGHM and in animals in which the change is secondary to hypertension, it may be reasonable to ask whether the vessel wall mechanisms controlling mass and cell replication are linked at some fundamental level.

Our data also suggest that substantial elements of vascular structure are either genetic or at least fixed before birth and do not adapt to the changes effected by growth hormone elevation. For example, despite significant aortic wall mass increases in the presence of excess growth hormone, there was no effect on the number of layers of elastin in the aortic wall. Wolinsky and Glagov studied wall structure and dimensions in several different species and found that, as body mass increased, the radius of the aorta also increased. However, wall stress per unit cross-sectional area was kept within a constant range by increasing the number of layers in the aortas to make a thicker wall. In contrast, where wall tension changed in hypertension, wall thickness increased without changing the number of layers. Developmental studies generally show that the number of layers of elastin in the aorta is determined around birth whereas growth hormone is not an active promoter of animal growth until 2–3 weeks after birth. Our data would support the hypothesis that constant wall stress is maintained by changing thickness of layers, whereas the number of layers in the aorta are controlled by evolutionary processes that are determined either genetically or by as yet unclear events occurring during intrauterine development.

Another element of vascular structure that is under apparent genetic or prenatal control is probably of more relevance to the ontogeny of hypertension. The total number of vascular branches in resistance vessels conducting blood to the small intestine was the same in the TGHM and control animals. If, as above, we assume that more blood flow is required to perfuse a larger TGHM small intestine mass, we would predict that, in the presence of constant pressure, the TGHM would maintain a wall-to-lumen ratio at a constant level but would have larger lumens and thicker walls than the control vessels. This was not the case; wall-to-lumen ratio was greater in TGHM vessels, a characteristic more typically associated with the hypertensive vascular

respondingly increased and the vasculature must remodel to supply an increased blood flow.

We already know from studies in rats that cardiac output increases in response to chronic growth hormone elevation. In cardiac or renal hypertrophy there are corresponding increases in blood flow to the hypertrophic organ, and as stated above, the vessel wall remodels to provide an increased lumen size and thickened wall. However, if the increase in body mass (1.7-fold) predicts a blood flow that would only require an increase in aortic radius of 14% greater than the controls. We did see a significant increase in wall thickness (24%). However, the aortic wall-to-lumen ratio was not elevated in the TGHM. Again, this is similar to Gothberg and Folkow’s study of renal hypertrophy after unilateral nephrectomy. Under these conditions, in the absence of blood pressure changes, vessels undergo both a dilatation of the lumen and an increase in wall thickness, but the wall-to-lumen ratio does not change, and a constant wall stress is maintained. Thus, the aorta of the TGHM resembles an artery supplying a hypertrophic organ rather than a hypertensive vessel that typically would have an increased wall-to-lumen ratio.

The small intestine and mesenteric vessels supplying it were larger in transgenic animals, but the number and branch pattern of the mesenteric vessels was constant.

Thus, the aorta of the TGHM resembles an artery supplying a hypertrophic organ rather than a hypertensive vessel that typically would have an increased wall-to-lumen ratio.
bed.4,18 We have considered two hypotheses to explain this phenomenon: 1) Vascular resistance in the mesenteric network may be controlled in a segment-specific fashion such that some segments contribute more to resistance and, therefore, show disproportionate structural modifications during remodeling. Physiological studies have recently shown that only vessels in the segment with the highest flow rate contributed greatly to resistance in the rat cremasteric network.33 Furthermore, vascular remodeling in the cerebral34 and cremasteric35 networks in response to renal hypertension also occurs in a segment-specific fashion. Presumably, these segments are responsible for autoregulatory control of blood flow in the presence of elevated systemic pressure as proposed by Cowley.36 This hypothesis would suggest that, under conditions of presumably increased flow in the TGHM, extra work must be distributed to the mesenteric vascular tree to dissipate power to levels appropriate for capillary exchange in the intestine. These altered rheological conditions are translated locally to a greater wall mass relative to the change in lumen diameter and in a segment-specific fashion because these animals are unable to change network branch patterns. A detailed analysis of the segmental distribution of resistance and structural changes in TGHM could provide a unified explanation for focal wall thickness increases in hypertension and in the TGHM. 2) There may also be a segment of the vascular network that is susceptible to a direct effect of growth hormone or other circulating endocrine factors. Such an effect might be exacerbated at sites where the vessel wall was specially adapted to provide contractile regulation of flow. In support of this hypothesis, we might note that, although the data did not reach significance, the wall-to-lumen ratio of the cerebral vessels of TGHM was, on average, greater than control vessels. Perhaps our failure to see a difference represents sampling problems in a complex vascular tree.

Finally, we would like to suggest that the absence of a measurable difference in blood pressure in the TGHM compared with the control could be misleading. In terms of Folkow's hypothesis,4 a thick-walled vasculature should respond to an agonist with a greater contractility, larger resistance elevation, and, therefore, hypertension. A simple explanation is suggested by the observation that hypertension in humans with excess growth hormone is restricted to only a portion of that population.1-3 It is conceivable that vascular mass changes similar to those described here could combine with other factors modulating hypertension, either genetic factors or environmental factors, to produce increased propensity for elevated blood pressure.3 Indeed, Folkow et al.37,38 have recently shown that hypothalamic animals requiring growth hormone supplementation to structurally remodel in response to hypertension, but Harrap et al.39 have added that growth hormone supplementation alone in a normal animal does not lead to blood pressure elevations. It is clear from these results that growth hormone or IGF-1 is required but not sufficient to produce structural changes in the vasculature. Our own data suggest that structural alterations alone, in the presence of growth hormone elevation, are not sufficient to produce hypertension. Furthermore, it has been reported by Lee et al.19 that relaxed lumen diameters in small mesenteric arteries of spontaneously hypertensive rats are not different, despite significantly increased wall mass. Although the result of this morphometric study is difficult to interpret because of the likely errors with this method, as discussed above, these data suggest that elevated resistance may occur due to a greater active wall tension generated by a larger wall mass, in agreement with Folkow's hypothesis.4 Therefore, it would be very interesting to know how the TGHM would respond to various hypertensive regimens or to interbreeding with other mouse strains with the genetic propensity for hypertension.39

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References


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