Heparin inhibits mesenteric vascular hypertrophy in angiotensin II-infusion hypertension in rats

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Abstract

Objective: Chronic infusion with angiotensin II increases blood pressure and activates growth mechanisms to produce hypertrophy of the heart and vessels. In order to better understand mechanisms of angiotensin II induced vascular hypertrophy, this study aimed to determine whether heparin, a potent inhibitor of smooth muscle proliferation mechanisms, was able to inhibit vascular hypertrophy.

Methods: Angiotensin II (100, 200 or 300 ng/min/kg s.c.) or a saline vehicle control were infused into rats for 14 days. A separate group of animals were co-infused with heparin (0.3 mg/h/kg i.v.) and angiotensin II (200 ng/min/kg s.c.) to test whether hypertension or hypertrophy were antagonized. Blood pressure was measured by tail cuff method and vessel media cross sectional area was measured by morphometry in aorta and mesenteric arteries.

Results: Blood pressure elevation and cardiovascular hypertrophy produced by angiotensin II were strongly dose-dependent. Hypertrophy responses at 14 days of treatment also appeared to be influenced partly by local factors as medial cross sectional area was increased more in mesenteric arteries than in thoracic aorta, and left ventricle weight was least affected. Heparin treatment did not influence the increase of blood pressure in angiotensin II infused animals, but the mesenteric vascular hypertrophy response due to angiotensin II was inhibited by approximately 50%. Inhibition of a modest cardiac hypertrophy and aortic medial hypertrophy did not reach significance. These data suggest that heparin interferes directly with the hypertrophy mechanism in mesenteric arteries, and that heparin-sensitive growth mechanisms are important in mediating angiotensin induced mesenteric vascular hypertrophy.

Conclusions: Angiotensin II infusion produced vascular medial hypertrophy and increased blood pressure, however the inhibitory effect of heparin on hypertrophy in mesenteric arteries was not mediated through angiotensin II induced vasoconstriction or blood pressure elevation. These data suggest that heparin interferes directly with the hypertrophy mechanism in mesenteric arteries, and that heparin-sensitive growth mechanisms are important in mediating angiotensin induced mesenteric vascular hypertrophy.

Keywords: Hypertension; Hypertrophy; Smooth muscle; Heparin; Rat; Angiotensin II

1. Introduction

Chronic infusion of the vasoconstrictor angiotensin II produces hypertension [1] and is associated with cardiac and vascular hypertrophy [2,3]. Angiotensin II also promotes growth of vascular smooth muscle cells in culture, suggesting that specific cellular growth mechanisms, independent from blood pressure elevating effects, are involved in mediating the hypertrophy responses. A fundamental role for angiotensin II in regulating vascular smooth muscle growth is indicated by the finding that DNA synthesis in injured rat carotid arteries is also increased by angiotensin II infusion [3] and inhibited by angiotensin converting enzyme (ACE) inhibitors [4] and angiotensin II receptor antagonists [5]. The mechanisms by which angiotensin II promotes growth have not been fully elucidated, but increases in protein [6–8] and DNA synthesis [9,10] in angiotensin II stimulated cultures are associated with increased expression of cellular growth factors [10,11] and growth factor receptors [10], while growth can be inhibited by interfering with autocrine growth mechanisms [12]. Similar mechanisms may be activated in vivo where
infusion of angiotensin II also reportedly increases aortic growth factor and receptor mRNA expression [13,14] and DNA synthesis [3,15]. In mesenteric vessels of angiotensin II infused rats there is activation of DNA synthesis and increased expression of extracellular matrix genes [16].

Much of our knowledge on angiotensin II induced growth mechanisms has come from aortic smooth muscle cells in culture, however the consequences of angiotensin II induced growth are of greatest significance to hypertension in the resistance vasculature in vivo. Folkow [17] has suggested that hypertrophy of these vessels creates an amplifier of constrictor mechanisms, producing greater increases in resistance and thus promoting the development of hypertension. The importance of angiotensin II in creating these amplifiers is indicated in studies with angiotensin converting enzyme inhibitors [18,19] and angiotensin II receptor antagonists [20,21] in primary hypertrophy. Development of abnormal vascular amplifiers [18,20] and hypertrophy [19,21] in spontaneously hypertensive rats is prevented and hypertension is ameliorated when animals are treated with these angiotensin II lowering or receptor antagonising drugs. However, the effect of angiotensin II in these experiments is confounded by the effect of blood pressure lowering and so growth mechanisms which are regulated by wall tension may also be significant contributors to smooth muscle growth control in these circumstances.

The role of angiotensin II in hypertrophy may be more directly tested by examining the influence of growth inhibitors during development of hypertension, without involving blood pressure directly. The anticoagulant heparin is a potent smooth muscle growth inhibitor [22] and heparin-like glycosaminoglycans secreted from endothelium [23] and smooth muscle cells [24] are thought to play a role in regulating cell replication in the vessel wall [22,25]. Vascular growth may result from an alteration in the normal balance of inhibitory and stimulatory influences in the vessel wall. For example, removal of the endothelium with a balloon catheter leads to exposure of smooth muscle cells to mitogenic influences from adhering platelets and other cells in the vessel wall, but regrowth of the endothelium appears to restore growth inhibition [22,25]. Heparin infusion into injured vessels mimics this growth inhibition capacity in some vascular repair models [22]. It is not known whether the interaction between growth stimulation and growth inhibition is important in angiotensin II induced vascular hypertrophy. Vascular injury studies have shown that growth inhibitory effects of heparin and ACE inhibitors [26] are additive, suggesting that angiotensin II and heparin may affect growth through different mechanisms. However, heparin may inhibit proliferation of vascular smooth muscle cells by altering the activity of growth factors [27,28] or growth inhibitors [29] which are regulated by angiotensin II in cultured cells. The aim of the present study therefore was to examine whether heparin infusion is able to inhibit the development of vascular hypertrophy in angiotensin II induced cardiovascular growth.

2. Methods

2.1. Animal models

Male Wistar Kyoto rats from a colony established at the Baker Institute received subcutaneous infusion of angiotensin II (Sigma Chemical, St. Louis, MO) from osmotic minipumps (Alza, Palo Alto, CA) for 14 days. Animals at 6 weeks of age received either 100 (LD), 200 (MD) or 300 (HD) ng/min/kg body weight angiotensin II (Sigma Chemical, St Louis, MO) infused at a rate of 2.5 μl/h. There were 6 rats in each group. Seven age-matched control rats were infused with vehicle (0.9% saline) in the same way. Heparin (Sigma Chemical, St. Louis, MO) was infused from separate osmotic minipumps via a catheter into the right jugular vein. In this experiment there were four groups of rats, with osmotic minipumps delivering either saline vehicle (n = 7), heparin (0.3 mg/h/kg) plus saline (n = 8), angiotensin II (200 ng/min/kg) plus saline (n = 8) or angiotensin II plus heparin (n = 7) for 14 days. Surgical procedures were approved by the Baker Institute and Alfred Hospital Animal Experimentation Committee and conformed to National Health and Medical Research Council of Australia guidelines. After three days recovery, systolic blood pressure was measured in conscious rats on an automated multi-channel system (ITC Life Science Instruments, Woodland Hills, CA) with tail cuffs to constrain caudal artery flow and photoelectric sensors to detect the tail pulses as cuff pressure was reduced. Animals were maintained at approximately 27°C for 10–20 min to encourage caudal artery vasodilatation.

2.2. Tissue collection

At 2 weeks after pump placement the rats were anaesthetized (Pentobarbitone, 60 mg/kg, i.p.) and the abdominal aorta was cannulated for perfusion of the mesenteric circulation with fixative. Immediately prior to perfusion the heart and descending thoracic aorta (between left subclavian artery and diaphragm) were removed. The atria were discarded and the remainder of the heart was separated into right ventricle and left ventricle plus septum before weighing. The thoracic aorta was cleared of adherent fat and intercostal arteries, weighed and then a ring 2–3 mm long was taken from the distal end of the aorta and placed into fixative (2.5% glutaraldehyde in 0.1 mol/l phosphate buffer, pH = 7.4) for later morphometric analysis.

2.3. Morphometry

The mesenteric circulation was perfused with Hank’s balanced salt solution containing papaverine (0.1 mg/ml)
and heparin (2.5 units/ml) for 5 min at 1 ml/min/100 g body weight, then with 2.5% glutaraldehyde in 0.1 mol/l phosphate buffer (pH = 7.4) for 10 min at the same flow rate. The mesenteric bed was removed and immersed in fixative overnight. Four vessel segments were taken from the third branch order vessels proximal to the intestinal margin (approximate inner diameter of 250 μm) for embedding in epoxy resin (Polarbed, Polaron, Watford, Herts, England). Cross sections from the thoracic aorta and four mesenteric vessels were cut and stained with toluidine blue in 1% Borax. Images of thoracic aorta and mesenteric artery cross sections were projected onto a digitising tablet and areas bounded by inner and outer elastic laminae were measured using a custom made morphometry software package. Medial area was calculated as the difference between the two values. In all vessels studied the intima consisted of only a single layer of endothelium, which contributed very little to the vessel cross sectional area measurement, and so the lumen area was calculated as that bounded by the inner elastic lamina.

2.4. Statistics

Group comparisons were made by one way analysis of variance for the angiotensin dose experiment and two way analysis of variance for the heparin inhibition experiment. Individual treatment effects were analyzed by orthogonal partitioning of the sums of squares [30] into angiotensin II dose effects, and for the heparin inhibition experiment into effects of angiotensin II, heparin and an interaction term (Sigmastat, Jandel Scientific, San Rafael CA, USA). Comparisons between individual groups were made by Bonferroni correction.

Table 1
Cardiac and aortic weights in WKY rats after 2 weeks of angiotensin II-induced hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Angiotensin II infusion rate (ng/min/kg)</th>
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<td></td>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Left ventricle weight (mg)</td>
<td></td>
<td>652 ± 25</td>
<td>676 ± 27</td>
<td>711 ± 24</td>
<td>722 ± 62</td>
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<tr>
<td>Left ventricle/Body weight (mg/g)</td>
<td></td>
<td>2.64 ± 0.06</td>
<td>2.79 ± 0.10</td>
<td>2.96 ± 0.09</td>
<td>3.69 ± 0.25*</td>
</tr>
<tr>
<td>Thoracic aorta weight (mg/cm)</td>
<td></td>
<td>9.24 ± 0.42</td>
<td>10.16 ± 0.36</td>
<td>10.86 ± 0.65*</td>
<td>11.39 ± 0.51*</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td>247 ± 7</td>
<td>243 ± 4</td>
<td>241 ± 6</td>
<td>195 ± 9*</td>
</tr>
</tbody>
</table>

* P < 0.05 for difference with control (0 ng/min/kg).

n = number of animals.
3. Results

3.1. Effects of angiotensin II treatment

3.1.1. Blood pressure, cardiac hypertrophy and body weight

Systolic blood pressure increased rapidly within the first three days of angiotensin II infusion (Fig. 1), and by 6 days all three treatment groups were significantly higher than the control group (P < 0.01). The blood pressure reached was highly dose-dependent with analysis of variance for treatment dose effects being significant at P < 0.01 at both 6 days and 14 days. The mean value for LD rats after 14 days angiotensin II infusion was 32 mm Hg greater than control, MD was 51 mm Hg greater than control and HD was 76 mm Hg greater than control.

Left ventricle weight increased significantly (P < 0.05, ANOVA) with increasing rate of angiotensin II infusion (Table 1), however these effects were only small in magnitude (4–11%) and did not reach significance when Bonferroni’s t test was used (Table 1). There was also a significantly dose related increase in the left ventricle/body weight ratio, however in HD rats body weights were significantly lower (Table 1), such that an 11% increase in left ventricle weight and a 21% decrease in body weight produced a 40% increase in left ventricle/body weight ratio (LV/BW). The body weight was not affected in MD and LD groups and the increase in LV/BW (5% and 12% respectively) was due to the increase in left ventricle weight (4% and 9%).

3.2. Vascular hypertrophy

Thoracic aorta weight/length also increased significantly with increasing dose of angiotensin II; being 10%, 18% and 23% in LD, MD and HD respectively (Table 1). These percentage increases were twice as large as the LV weight increases. Angiotensin II significantly increased the mass of smooth muscle tissue in the aorta, as cross sectional area of the media in thoracic aorta was significantly larger than controls in all three angiotensin treatment groups (Fig. 2A) and these increases (23% LD, 25% MD, 53% HD) were approximately four-fold more than the LV weight increases. This suggests that angiotensin II infusion was a more potent activator of hypertrophy mechanisms in aortic smooth muscle than in the heart of the same animals.

The mesenteric vasculature showed the greatest hypertrophy responses to angiotensin II infusion (Fig. 2B); again these changes were significantly dose-dependent with the medial cross sectional area in LD rats 32% larger than controls, in MD 54% larger and in HD rats 88% larger. There was also a significant increase in media/lumen area ratio in the mesenteric vessels (LD 44%, MD 37%, HD 59%), but no significant effect on lumen cross sectional area (control 45.2 ± 2.6 × 10^-3 μm², LD 45.3 ± 4.3 × 10^-3 μm², MD 54.1 ± 2.6 × 10^-3 μm², HD 58.5 ± 6.3 × 10^-3 μm²; P > 0.05). As in aorta, the effect of angiotensin II infusion on medial cross sectional area and media/lumen ratio was greater than its effect on LV weight or LV/BW ratio.

3.3. Effects of heparin treatment

Analysis of variance was used in this study to test for significance of an angiotensin II effect and the influence of heparin on this effect. Data are presented as mean ± SEM. A P value less than 0.05 was considered significant.

Table 2
Influence of heparin infusion on cardiac and aortic weights, body weight and hematocrit in WKY rats after 2 weeks of angiotensin II-induced hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline</th>
<th>Heparin</th>
<th>ANOVA</th>
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<tr>
<td></td>
<td>Vehicle</td>
<td>Heparin</td>
<td>Angiotensin</td>
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<td>8</td>
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<tr>
<td>Left ventricle weight (mg)</td>
<td>629 ± 14</td>
<td>617 ± 11</td>
<td>701 ± 23</td>
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<tr>
<td>Left ventricle weight/body weight (mg/g)</td>
<td>2.29 ± 0.05</td>
<td>2.29 ± 0.03</td>
<td>2.82 ± 0.13</td>
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<tr>
<td>Thoracic aorta weight (mg/cm)</td>
<td>8.90 ± 0.14</td>
<td>8.54 ± 0.32</td>
<td>11.65 ± 0.61</td>
</tr>
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<tr>
<td>Hematocrit (%)</td>
<td>44.1 ± 0.9</td>
<td>42.3 ± 1.6</td>
<td>44.3 ± 1.2</td>
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<tr>
<td>Body weight (g)</td>
<td>275 ± 5</td>
<td>268 ± 5</td>
<td>251 ± 7</td>
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</table>

* P < 0.05 for significant effect, ns not significant.

n = number of animals.
heparin on responses to angiotensin II infusion. Angiotensin II infused for 14 days increased blood pressure (Fig. 3) and slightly lowered body weight (Table 2), but did not affect hematocrit (Table 2). Heparin had no significant effect on blood pressure, body weight or hematocrit, either in the presence or absence of angiotensin II.

Consistent with the blood pressure data, heparin treatment had no significant effect on left ventricle weight/body weight ratio (Table 2), while the angiotensin II effect was significant, increasing LV/BW by 23% when infused alone, and by 12% in the presence of heparin. This 50% reduction in cardiac hypertrophy response was largely due to a small protective effect of heparin infusion on the body weight-reducing effects of angiotensin II infusion; there were no significant effects on left ventricle weight. Aorta weight also increased significantly with angiotensin II (31%), while heparin had no significant effect, as a 23% difference remained between heparin treated and angiotensin II treated groups (Table 2). Angiotensin II infusion induced a 30% hypertrophy (saline vs. ang II) of the medial layer of the aorta and although heparin infusion reduced the difference in means by approximately 50% (30% vs. 16%), the analysis of variance showed no significant interaction term \( P = 0.19 \) and the effect of heparin did not reach significance \( P = 0.071 \). There was no significant effect of heparin treatment in the non-hypertrophied vessels of saline infused rats (Fig. 4A).

In mesenteric vessels (Fig. 5), heparin inhibited the medial cross sectional area increase due to the angiotensin II infusion by approximately 50% (65% vs. 34%, Fig. 4B), whereas there was no effect of heparin in saline treated animals. This was reflected in the ANOVA as significant effects due to angiotensin II and heparin (Table 3), but also with a significant interaction term \( P < 0.05 \), indicating that heparin had specific effects on the angiotensin II induced hypertrophy responses but none on heparin-treated controls. Despite these significant reductions in medial hypertrophy responses by heparin in angiotensin II treated animals, mesenteric artery medial area remained significantly greater than in heparin treated controls (Fig. 4B). In the ANOVA of lumen cross sectional area measurements, angiotensin treatment tended to increase lumen size and

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**Fig. 4.** Effects of angiotensin II (200 ng/min/kg) and/or heparin (0.3 mg/h/kg) infusion on vascular morphometry measurements (A) media cross-sectional area in thoracic aorta, (B) media cross-sectional area in mesenteric arteries and (C) media/lumen area ratio in mesenteric arteries after 2 weeks of treatment. * P < 0.05 compared to vehicle treated control group. † P < 0.05 compared to angiotensin II treated group.

**Fig. 5.** Photomicrographs of mesenteric vessel cross sections from (A) saline, (B) angiotensin II and (C) heparin plus angiotensin II treated animals. (toluidine blue stain, bar = 100 μm).
heparin tended to decrease lumen size (Table 3), but there was no significant interaction term (control 49.4 ± 2.5 × 10^3 μm^2; heparin 44.3 ± 2.2 × 10^3 μm^2, angiotensin II 54.7 ± 2.2 × 10^3 μm^2; heparin 50.1 ± 1.7 × 10^3 μm^2; P > 0.05). The media/lumen ratio increase due to angiotensin II was also significant, and the increase in means was 60% lower in the presence of heparin (37% vs. 14%, Fig. 4C), however these data were more variable than the media cross sectional areas and neither the heparin effect nor the interaction term reached significance (Table 3).

4. Discussion

The major finding of this study was that infusion of heparin specifically inhibited the mesenteric vascular hypertrophy induced by angiotensin II infusion. The inhibition was apparently selective for the vascular hypertrophy induced by angiotensin II infusion. The inhibitory effect of heparin specifically inhibited the mesenteric vascular hypertrophy induced by angiotensin II and wall stress due to blood pressure elevation produce only a relatively small cardiac hypertrophy at this time. In contrast, the mesenteric vasculature and the aorta had a large and strongly dose-dependent hypertrophy. The extent of hypertrophy, in the presence of even relatively modest pressure elevations in LD treatment, supports a more direct influence of angiotensin II infusion on medial smooth muscle cells. It is not unreasonable to expect a direct action of angiotensin II to produce medial hypertrophy in vivo, given its effects on smooth muscle cellular [6] and extracellular protein [8] production, leading to cellular hypertrophy [7] or hyperplasia [9] in vitro. These effects might be mediated by a direct influence on cellular growth mechanisms, as exposure to angiotensin II leads to increased expression of proto-oncogenes myc and fos [33] as well as increased PDGF [10,12,34] and PDGF receptor expression [10]. TGF-β expression is also increased [9,12] and interference with bFGF and TGF-β1 mRNA production with anti-sense oligonucleotides decreases or increases the growth responses respectively [12]. Angiotensin II in vivo might stimulate similar mechanisms, as acute angiotensin II infusion also produces a small but rapid increase in PDGF B chain mRNA in the vascular wall [13] and chronic infusion of angiotensin II increases EGF receptor expression and ligand binding along with increasing the rate of smooth muscle cell DNA synthesis [3,14]. Further study is necessary to determine whether some or all of these mechanisms are activated in resistance vessels.

In the present study, heparin was found to inhibit the mesenteric vascular growth mechanisms activated by angiotensin II infusion by an average of approximately 50%. Thus, the magnitude by which heparin inhibited mesenteric vascular hypertrophy was similar to that which it inhibits proliferative neo-intima formation after removal of endothelium [22]. Wiener et al. [16] have shown that angiotensin II infusion produces significant medial PCNA expression, indicating DNA synthesis in mesenteric vessels and Black et al. [35] have found that mesenteric vessel medial hypertrophy due to angiotensin II infusion occurred predominantly by hyperplasia in spontaneously hypertensive rats. Together with the present study, these findings suggest that heparin is able to inhibit smooth muscle cell proliferative responses in the absence of endothelium after injury and in the presence of intact endothelium in these mesenteric arteries of hypertensive rats.
The mechanism of heparin action in reducing smooth muscle hyperplasia both in vivo and in vitro remains unknown, despite considerable interest in the last decade and a half. Heparin may act by depleting the local activity of secreted heparin-binding growth factors, for example heparin binds PDGF A chain and inhibits its mitogenic activity [27]. Heparin also inhibits bFGF stimulated growth responses of endothelial and smooth muscle cells [28,36] and is able to deplete the amount of bFGF present in the wall of injured vessels [28]. Alternatively, heparin may increase activity of a growth inhibitor, as it increases the activity of TGFβ [29] in cultured cells, which is capable of inhibiting smooth muscle proliferation and encourages cellular hypertrophy [29,37]. Clowes et al. have shown that heparin also directly inhibits smooth muscle cell matrix degradation and inhibits replication following vascular injury [38,39]. Part of heparin’s growth inhibitory effects might be mediated by inhibition of intracellular kinases involved in signal transduction [40] and regulation of transcription activator proteins [41]. These data come from experiments in vitro or injury studies in vivo, and so the contribution of each of these mechanisms to vascular growth inhibition in hypertension is unknown, yet our data are supportive of a role for alterations in this angiotensin II infusion model of the balance between growth stimulation and inhibition involving heparin-like compounds secreted by endothelium and smooth muscle. Recent evidence has shown that the extracellular matrix is altered in mesenteric blood vessels of angiotensin II infused rats [16] as part of the hypertrophy mechanism in this model. More specific studies on alteration of growth regulatory matrix components in these vessels may be worthwhile to determine if increases in growth stimulators and/or growth inhibitors are involved in the hypertrophy process.

Heparin treatment inhibited the vascular hypertrophy produced by angiotensin II infusion but the hypertensive effects of angiotensin II infusion remained. Similar separation of vascular hypertrophy and blood pressure elevation in angiotensin II infusion models occurs in hydralazine treated rats, where blood pressure elevation is prevented without affecting vascular hypertrophy [2], and in prazosin treated rats, where DNA synthesis is reduced without affecting blood pressure [17]. These studies do not appear to support the hypothesis that a slow pressor effect of angiotensin II [42] is solely due to hypertrophy of the resistance vasculature and development of vascular amplifiers. However continued elevation of blood pressure may be due to secondary effects of angiotensin II infusion, such as those documented in the kidney [43], or as suggested by the effects of prazosin, the enhancement of sympathetic activity by angiotensin II [15]. It is not yet known whether these also are affected by heparin. Interestingly, heparin treatment is reported to have antihypertensive effects in stroke prone spontaneously hypertensive rats [44], spontaneously hypertensive rats (SHR) and one-kidney one clip Goldblatt hypertension in rats [31]. This has been partly attributed to lowering of hematocrit [31,44], although we did not find this in our study, perhaps due to differences in the dose of heparin administered, or to the continuous administration of heparin by osmotic mini-pump rather than by the acute high doses produced by injection. These effects are not due to the anticoagulant properties of heparin as non-anticoagulant fractions of heparin are equally effective in lowering blood pressure [45]. Heparin is not a direct vasodilator [46] and has no effect on blood pressure responses to acute angiotensin II infusion [46]. However, heparin treatment raises plasma renin levels and paradoxically inhibits angiotensin converting enzyme activity [31,47], resulting in lowered plasma angiotensin II levels. Absence of an effect of heparin on blood pressure in the present study would suggest that the circulating renin angiotensin system was not significantly altered in this model. In the angiotensin II infusion group, blood pressure was likely maintained by the elevated angiotensin II levels produced by constant infusion. We cannot exclude an effect of heparin on local tissue formation of angiotensin II. Taken together this data is consistent with heparin having a separate and direct effect on vascular wall hypertrophy mechanisms in hypertension, independent from any effects on blood pressure.

In conclusion it has been shown that angiotensin II infusion has increased blood pressure and induced widespread cardiovascular hypertrophy by a dose-dependent mechanism. The anti-trophic effect of heparin was not dependent on blood pressure lowering, implicating a more direct mechanism of hypertrophy in this model, possibly involving either increased growth stimulation or decreased growth inhibition. The finding that heparin can effectively inhibit hypertrophy might provide a promising avenue for clinical intervention in the vascular changes due to acute hypertension and more specifically to the growth processes mediated via angiotensin II formation. Low molecular weight heparin fractions, with lowered anticoagulant activity but equivalent effect on experimental smooth muscle cell growth [48] may be worth further exploration in this regard. The mechanism of vascular hypertrophy induced by angiotensin II infusion is not known, but our data show that it includes heparin-sensitive elements, suggesting that vascular wall mass may in part be regulated by the heparin-like molecules normally present in the vessel wall.

Acknowledgements

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References


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