Congenic strains reveal the effect of the renin gene on skeletal muscle angiogenesis induced by electrical stimulation

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Submitted 11 July 2007; accepted in final form 14 January 2008

The importance of the renin-angiotensin system (RAS) in controlling sodium homeostasis and vascular resistance is well established; however, in the past decade, much attention has been focused on the importance of angiotensin II (ANG II) as a regulator of microvessel density. Studies from our laboratory (2–4, 15, 37, 42) over the last 5 years have shown that ANG II is an essential component of the control system regulating microvessel density in the skeletal muscle. We have shown that inhibition of RAS activity with the use of pharmacological blockers of ANG II formation and blockade of the angiotensin type 1 (AT1) receptor significantly attenuated the skeletal muscle angiogenic response of normotensive rats induced by exercise (3) and electrical stimulation (2). In addition, we found (37) that chronic infusion of ANG II, at subpressor doses, completely restored the angiogenesis response induced by electrical stimulation in rats fed a high-salt diet. The effects of high salt on microvascular structure and function in the absence of hypertension have been largely attributed to the suppression of RAS activity by inhibition of renal renin release. Maintenance of normal circulating levels of ANG II in high-salt-fed animals by exogenous infusion has been associated with restoration of normal arteriolar reactivity responses (55) and prevention of high-salt-induced capillary rarefaction (26).

Dahl S and SS/Mcw rats represent a low-renin model of hypertension, which is associated with reduced microvascular density (rarefaction) (6) and an impaired ability to regulate their RAS, leading to chronically low ANG II levels, even when the rats are on a low-salt diet (3, 14). We have observed that the impaired renin regulation in SS/Mcw is associated with an impaired angiogenic response induced by electrical stimulation. The transfer of part (10 cM) of chromosome 13 (containing the renin gene) from a Dahl salt-resistant (Dahl R) rat onto a Dahl S rat restored normal plasma renin response as well as the increased vascular endothelial growth factor (VEGF) expression and the angiogenic response induced by electrical stimulation (4). In a number of studies, various combinations of congenics of the SS and SR renin alleles have been tested for the ability to regulate renin. The genomic sequence of the coding regions and the immediate 5′-flanking regulatory region for the renin gene of SS and normotensive SR rats are identical (1), although plasma renin activity (PRA) is reduced and angiogenesis is impaired in the SS rat compared with the SR and the SS/ren (RR) congenic rats (4, 27). We recently found (15) that the transfer of the chromosome 13 from a strain that does not share the antiangiogenic phenotype with the SS/Mcw, the Brown Norway (BN) rat, consistently restored the angiogenic response induced by electrical stimulation. Sequencing studies performed in our laboratory of the coding and 5′-flanking promoter regions in the renin gene of the rat demonstrated that the three strains (BN, SS, and SR) had identical sequences in this region. Although deletions and sequence variants at different sites in the intronic regions and in the distant 5′- and 3′-flanking regions of the SS rat have been described compared with the SR rat (54), these variants or differences in alleles at a closely linked locus have not been tested for functional relevance with regard to renin expression. Together, these results suggest the existence of a mutation that interacts with the renin gene in the SS/Mcw rat and may be related to the antiangiogenic phenotype. To identify genomic regions that impact the regulation of renin and thus the angiogenic response in the SS/Mcw rat, we developed a unique set of congenic rats that included or excluded the renin locus. In parallel, a series of in vitro and in vivo experiments including the use of angiotensin-converting enzyme (ACE) inhibitor,
ANG II infusion, and changes in dietary salt content were performed in dietary salt content were performed to validate the effect of the RAS on the angiogenic response induced by electrical stimulation in SS/Mcwi and consomic SS-13BN/Mcwi rats.

The generation of the congenic strains combined with the pharmacological studies provides new insight into how renin regulates microvascular density in skeletal muscle and strongly suggested that RAS disregulation plays a critical role in the attenuation of the microvascular angiogenesis in the salt-sensitive hypertensive SS/Mcwi rat. Understanding how disregulation of renin impacts angiogenesis in the SS/Mcwi rat may shed light on the reduction in vessel density that occurs in several forms of low-renin hypertension in humans (25, 31, 45).

MATERIALS AND METHODS

Animals. The present study was performed in male SS/Mcwi rats and SS-13BN/Mcwi consomic rats from our colony at the Medical College of Wisconsin (MCW). The consomic rat line was derived by using inbred normotensive BN/SSNHsd/Mcwi rats and salt-sensitive hypertensive Dahl SS/JrHsd/Mcwi rats, referred to here as BN/Mcwi and SS/Mcwi strains, respectively, whose origin was described previously (13). Four chromosome 13 congenic strains were developed by crossing inbred salt-sensitive hypertensive SS/Mcwi rats with consomic SS-13BN/Mcwi rats, generated at MCW by marker-assisted breeding (14). After the first cross between SS/Mcwi and SS-13BN/Mcwi strains, rats from the F1 generation were intercrossed and genotyped for the selection of recombinant animals. The progeny was initially genotyped with 34 simple sequence length polymorphism (SSLP) markers distributed along chromosome 13 (see Fig. 1 for genomic position of markers), and congenic rats for the desired regions of the chromosome were selected for one more round of backcrossing and intercrossing to reach homozygosity in the target regions for further establishment and expansion of the congenic rat strains. In total, four generations of breeding were necessary for the development of the congenic strains from the consomic SS-13BN/Mcwi. Additional genotyping with six SSLP markers (D13rat123, D13Got22, D13Wox5, D13Got30, D13rat127, and D13rat179; genomic position shown in Fig. 1) was performed on the selected congenic strains to further define the flanking regions and to ensure the relative position with respect to the renin gene (Fig. 1). All the markers used were selected according to their position in genetic (SHRxBN and FHHxACI) and genomic (version 3.4) maps and predicted polymorphisms between the SS and BN strains (marker size information and strain polymorphisms can be found at rgd.mcw.edu). As demonstrated in Fig. 1, we developed a total of four congenic rat strains that included or excluded the renin locus: line A [SS.BN-(D13rat20-D13rat127)/Mcwi], line B [SS.BN-(D13rat91-D13rat179)/Mcwi], line C [SS.BN-(D13rat20-D13Got22)/Mcwi], and line D [SS.BN-(D13rat123-D13rat101)/Mcwi]. All rats were generated and housed at MCW.

Experimental protocol. All animal protocols were approved by the MCW Institutional Animal Care and Use Committee. Animals were housed and cared for in the MCW Animal Resource Center and were given food and water ad libitum. Rats were submitted to 7 days of electrical stimulation and received different treatment during the entire stimulation protocol, being randomly assigned to the following groups: SS/Mcwi rats and SS-13BN/Mcwi consomic rats fed on high-salt (4% NaCl) or low-salt (0.4% NaCl) diet; SS/Mcwi rats fed on high-salt (4% NaCl) diet and receiving ANG II infusion; and SS-13BN/Mcwi consomic rats fed on low-salt (0.4% NaCl) diet treated with lisinopril (100 mg/kg in drinking water). The congenic rats were fed with 0.4% NaCl diet (Dyets) and water ad libitum from weaning throughout the entire stimulation protocol.

**Fig. 1.** Illustration of the 4 congenic lines (lines A–D) created around the renin gene. All lines carry a SS/Mcwi rat background genome. The inserts from the Brown Norway (BN) rat chromosome are denoted by the solid black bars. The renin gene position is marked with a dashed line.

**Electrical stimulation surgery.** Rats were anesthetized with an intramuscular injection of a mixture of ketamine (100 mg/kg) and acepromazine (2 mg/kg). Under aseptic conditions, a subcutaneous incision was made over the thoracolumbar region, and the rats received a miniature battery-powered stimulator that was previously designed and validated for chronic studies (32). After 24 h of recovery, the ankle flexor muscles tibialis anterior (TA) and extensor digitorum longus (EDL) were stimulated by electrodes localized in the vicinity of the common peroneal nerve, with square-wave impulses of 0.3-ms duration, 10-Hz frequency, and 3-V potential. The contraction of those muscles was maintained for 8 h/day over a period of 7 consecutive days. The contralateral leg was used as a control, and all animals were euthanized 7 days after the onset of stimulation.

**Tissue harvest and morphological analysis of vessel density.** After 7 days of stimulation the animals were euthanized by an overdose of Beuthanasia solution (Sigma, St. Louis, MO), and the stimulated and contralateral unstimulated muscles were removed, rinsed in physio-
logical salt solution, and weighed. A 100-μg section was taken from TA muscle and immediately frozen in liquid nitrogen for Western blot analysis. The remaining TA and the EDL were lightly fixed overnight in 0.25% formalin solution and sectioned. From every animal, sections of EDL and TA were immersed in a solution of 25 μg/ml rhodamine-labeled Griffonia simplicifolia I (GS-I) lectin (Sigma). GS-I lectin preferentially labels capillaries and small arterioles/venules. After a 2-h exposure to GS-I lectin, the muscles were rinsed and mounted on microscope slides as previously described (24). The sections were visualized with a video fluorescence microscope system with epi-illumination (Olympus ULWD CD Plan, ×20 objective). Twenty representative fields were selected for study from each muscle section. Images were digitized and quantified with automated computer vessel counting as previously described (44).

**Plasma renin activity.** The method used for measurements of PRA was performed as previously described (45). Briefly, arterial blood was collected in tubes containing K2EDTA and immediately centrifuged at 1500 g and 4°C. The samples were thawed on ice, and neomycin sulfate (0.1%), phenylmethylsulfonyl fluoride (0.25%), and maleic anhydrate (0.2 mol/l) were added to 50 μl of sample to inhibit converting enzyme and protease activity. After generation ANG I concentration was determined by radioimmunoassay (45).

**Angiotensin II infusion.** SS/Mcwi rats fed a high-salt diet (4% NaCl) were continuously infused intravenously with ANG II or vehicle via the jugular catheter at a subpressor rate of ANG II (3 ng·kg⁻¹·min⁻¹), dissolved in sterile saline, throughout the 7-day electrical stimulation period, according to the protocol previously described (42).

**Data analysis and statistics.** For each muscle, the vessel counts of all the selected fields were averaged to a single vessel density. Vessel density was expressed in terms of mean number of vessel-grid intersections per microscope field (0.224 mm²). For each experimental group, the measured vessel density of the stimulated muscle was compared to its unstimulated counterpart. All values are presented as means ± SE. The significance of differences in values measured in the same animal was evaluated with a two-factor ANOVA (diet × stimulation) with repeated measures on one factor (stimulation). To evaluate the significance of differences in vessel density between stimulated and unstimulated sides, a one-way ANOVA was performed. Significant differences were further investigated with a post hoc test (Tukey’s).

**RESULTS**

Table 1 summarizes the body weight and muscle weight-to-body weight ratio of all groups analyzed. All rats were approximately the same age (8–10 wk) at the beginning of the experiment. Lisinopril-treated rats were significantly heavier than the control group before the start of drug infusion (307.88 ± 13.05 g control, 430.67 ± 4.25 g lisinopril; P < 0.05). Although the difference in body weight may reflect differences in animal age, previous studies in our lab have shown that the marked increase in vessel density induced by electrical stimulation is remarkably consistent in animals over the age range from 6 to 14 wk of age. All animals had a similar increase in body weight at the end of the experimental protocol, with the exception of rats treated with lisinopril, which had a decrease in body weight at the end of the experimental period. The reduced gain in body weight is a common event after ACE inhibitor therapy and may be related to loss of body fluid due to reduced ANG II and aldosterone levels. Electrical stimulation did not change muscle weight-to-body weight ratio in all groups analyzed.

Mean arterial pressure (MAP) of both groups (SS/Mcwi and SS-13B⁰/Mcwi rats) was similar when the rats were fed a low-salt diet (131.7 ± 2.12 and 132.5 ± 0.07 mmHg for SS/Mcwi and SS-13B⁰/Mcwi, respectively). When the high-salt diet was introduced to these animals, we observed that MAP only increased in the SS/Mcwi rats (Δ = 38.7 ± 4.7 mmHg), as shown in Fig. 2A. Transfer of chromosome 13 from the BN rat also restored the renin response to high-salt diet in the SS/Mcwi and SS-13BN/Mcwi, respectively).

<table>
<thead>
<tr>
<th>Congenic line</th>
<th>Start Weight</th>
<th>End Weight</th>
<th>BW/g</th>
<th>EDL/BW</th>
<th>TA/BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS/Mcwi-LS</td>
<td>231.8 ± 12.5</td>
<td>261.8 ± 16.4*</td>
<td>0.44 ± 0.01</td>
<td>1.84 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>SS/Mcwi-HS</td>
<td>247.5 ± 6.5</td>
<td>266.7 ± 6.4*</td>
<td>0.43 ± 0.02</td>
<td>1.74 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>SS-13BN-LS</td>
<td>307.9 ± 12.1</td>
<td>325.1 ± 9.5*</td>
<td>0.42 ± 0.01</td>
<td>1.85 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>SS-13BN-HS</td>
<td>285.0 ± 30.0</td>
<td>323.4 ± 28.2*</td>
<td>0.41 ± 0.02</td>
<td>1.68 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. TA, tibialis anterior; EDL, extensor digitorum longus; BW, body weight; U, unstimulated muscle; S, stimulated muscle. Groups were as follows: SS/Mcwi rats fed low-salt diet (SS/Mcwi-LS, n = 6); SS/Mcwi rats fed high-salt diet (SS/Mcwi-HS, n = 6); SS-13BN/Mcwi rats fed low-salt diet (SS-13BN-LS, n = 8); SS-13BN/Mcwi rats fed high-salt diet (SS-13BN-HS, n = 5); SS-13BN/Mcwi rats fed low-salt diet and treated with lisinopril (100 mg·kg⁻¹·day⁻¹) (SS-13BN-LSLIS, n = 6); SS/Mcwi rats with saline infusion (SS/Mcwi-saline, n = 6); SS/Mcwi rats with angiotensin (ANG) II infusion (SS/Mcwi-ANG II, n = 6); congenic line A (n = 6); congenic line B (n = 6); congenic line C (n = 7); and congenic line D (n = 10); *P < 0.05 vs. start weight.
Suppression of the RAS by high-salt diet significantly reduced the vessel density of the unstimulated muscles (34% and 16% for SS/Mcwi and SS-13BN/Mcwi rats, respectively) and also attenuated the angiogenic response induced by electrical stimulation in SS-13BN/Mcwi consomic rats (7% and 9% for EDL and TA, respectively; Fig. 2, B and C).

The significant increase in vessel density induced by stimulation in the TA (unstimulated 143.3 ± 2.9 vs. stimulated 166.8 ± 4.3 vessel-grid intersections/field, P < 0.05) and EDL (unstimulated 152.3 ± 3.8 vs. stimulated 165.2 ± 4.6 vessel-grid intersections/field, P < 0.05) muscles of SS-13BN/Mcwi rats fed on the low-salt diet was completely suppressed by lisinopril treatment (Fig. 3, A and B). In parallel, the angiogenic response was restored when the SS/Mcwi rats were placed on ANG II infusion during 7 days of electrical stimulation (unstimulated 105.8 ± 4.7 vs. stimulated 135.3 ± 4.7 vessel-grid intersections/field, P < 0.05; Fig. 3, C and D).

As represented in Fig. 1, the congenic strains that contain the BN renin gene, line A and line D, had a significant increase of 31–48% in vessel density in the TA and EDL muscles after electrical stimulation (Fig. 4). In contrast, congenic strains line C and line B, which did not have the BN allele for the renin gene, did not show this phenotype (Fig. 4). The smallest chromosome 13 insert (4.5 Mbp, line D) from the BN rat into the SS/Mcwi rats completely restored PRA (high salt 0.6 ± 0.1 vs. low salt 2.4 ± 0.3 ng ANG I·ml⁻¹·h⁻¹, P < 0.05; Fig. 5).

DISCUSSION

In the past years, several approaches have been developed to systematically decipher the gene–gene and gene–environment interactions that influence complex multigenic diseases, providing a dramatic impact on the medical and biological research fields. Our group is engaged in a powerful approach to dissect multigenic common diseases through the development of chromosome substitution techniques ranging from the whole chromosome (consomic rats) to very small chromosomal inserts (congenic rats). Identification of candidate regions of the genome, as well as genes within these regions, may bring new
insight into the genetic basis of pathways involved in disease susceptibility or resistant phenotypes.

Our lab has performed extensive studies to identify the gene or set of genes involved in the control of skeletal muscle angiogenesis, and several lines of evidence have indicated that the RAS plays a major role in the angiogenesis response induced by electrical stimulation (2, 4, 15, 42). The present study explored the effect of the renin gene on skeletal muscle angiogenesis with a consomic and a series of congenic rats that clearly demonstrate a positive association between the angiogenesis phenotype and the presence of a normally functioning renin gene.

Dahl S and SS/Mcwi rats represent a low-renin model of hypertension, which is associated with reduced microvascular density (rarefaction) (6) and impaired ability to regulate their RAS, leading to chronically low ANG II levels, even when the rats are on a low-salt diet (3, 14). Because of these characteristics, the Dahl S and SS/Mcwi rats represent a valuable animal model to study the physiological effects of the recovery of renin control mechanisms on the angiogenic response induced by electrical stimulation. The development of the consomic SS-13BN/Mcwi strain showed that the transfer of the entire chromosome 13 from the normotensive BN rat, containing a functioning renin gene, into the SS/Mcwi background completely restored the renin control mechanism and the angiogenic response after electrical stimulation (15). Since chromosome 13 contains a substantial number of genes in addition to the renin gene, narrowing the region of the chromosome that is responsible for maintenance of normal angiogenic responses provided additional support for the hypothesis that preservation of the normal regulation of the RAS plays a role in maintaining normal angiogenic phenotype. The increase in muscle vessel density after electrical stimulation was markedly improved by 43% in congenic line A, which contain a 6.8-Mbp region of the BN chromosome. This effect was still observed when the insert from the BN chromosome was reduced to 4.5 Mbp in line D. However, the vessel density response was dramatically suppressed in the strains that carried regions of the BN genome above (line C) or below (line B) the renin gene, with an increase in vessel density of only 7% and 4%, respectively, similar to what is found in the SS/Mcwi rats. Apparently, the impaired ability to regulate the RAS is corrected even when a shorter segment of chromosome 13 from the BN rat is substituted into the SS/Mcwi genetic background, since PRA was not

Fig. 3. Role of ANG II on the angiogenesis response after electrical stimulation. A and B: effect of lisinopril treatment on TA (A) and EDL (B) vessel density of SS-13BN/Mcwi rats fed low-salt diet. C and D: effect of ANG II infusion on TA (C) and EDL (D) vessel density of SS/Mcwi rats fed low-salt diet. Data are means ± SE for SS-13BN/Mcwi low salt (n = 8), SS-13BN/Mcwi low salt + lisinopril (n = 6), SS/Mcwi saline (n = 5), and SS/Mcwi ANG II (n = 6). *P < 0.05 vs. unstimulated muscle.
only higher in line D during a low-salt diet but was also normally regulated during dietary salt changes compared with SS/Mcwi rats. The smallest insert containing the renin allele from BN rat contains 51 known and 34 predicted genes, according to NCBI (Supplemental Table S1).1 The results clearly demonstrate that the transferred segment of chromosome 13 contains molecular variants with detectable effects on renin gene expression and angiogenesis. Thus, regardless of whether or not molecular variants in the renin gene itself or in genes linked to renin account for these findings, the present results are consistent with the hypothesis that genetically determined variation in the activity of the RAS may contribute to inherited variation in angiogenesis. This hypothesis is further supported by the physiological and pharmacological studies in the consomic SS-13BN/Mcwi strains, showing that the restoration of the angiogenic phenotype in SS-13BN/Mcwi rats after electrical stimulation was significantly attenuated when the RAS was inhibited by high-salt diet. In agreement with this, lisinopril treatment completely blocked the increase in vessel density in SS/Mcwi rats fed a low-salt diet. The role of ANG II in this effect was reinforced by the complete restoration of the skeletal muscle angiogenesis in SS/Mcwi rats infused with subpressor doses of ANG II.

In vivo and in vitro studies have shown that ANG II can induce neovascularization through different mechanisms including stimulation of endothelial cell proliferation and survival (35, 38) as well as increase in the expression of different growth factors including VEGF (12, 21, 43) and its receptor (47). As a result, ANG II has been involved in a number of angiogenesis-associated diseases such as retinal vascular disorders, including retinopathy of prematurity and proliferative diabetic retinopathy (17). Overexpression of renin in Ren-2 diabetic rats is associated with both retina and iris neovascularization that can be attenuated by RAS blockade via VEGF-dependent pathways (35).

A therapeutic role for RAS blockade has been suggested in the EUCLID study, in which the blockade of ANG II formation with lisinopril significantly slowed the progression of proliferative diabetic retinopathy (11). Studies have also shown that ACE inhibitors are potent inhibitors of experimental tumor development and angiogenesis. When used in combination with the conventional anticancer drugs, ACE inhibitors exert more potent antitumor activities compared with either single agent, in addition to suppression of the intratumoral angiogenesis (56). Studies suggest that this angiogenic effect may be associated with AT1 receptor activation. Tumor-associated angiogenesis is significantly impaired in AT1a-deficient mice. AT1 receptor expressed on tumor-associated macrophages mediates VEGF expression and angiogenesis (20). Another report showed that ANG II infusion increased capillary density in a hindlimb ischemia model with increased expression levels of VEGF and endothelial nitric oxide synthase (eNOS) (49). The role of NOS is also suggested as a possible downstream effector of the proangiogenic effect of AT1 receptor in the post-myocardial infarction neovascularization. The poor cardiac neovascularization found in AT1-deficient mice after myocardial infarction was associated with lower levels of matrix metalloproteinase and NOS activity as well as less inflammatory cell infiltration (51).

Recently, a growing number of studies have shown that variants of the human genes coding for renin, ACE, angio-

1 The online version of this article contains supplemental material.
Tensinogen, and the AT$_1$ receptor may be associated with complex multigenic diseases (41). The genetic variations involve the RAS that may affect the function of its components might have an influence on genetic predisposition to diabetes and renal and cardiovascular diseases (8, 9, 40, 46). A better understanding of the relationship between the ability to increase vessel density in response to physiological electrical stimuli in adult skeletal muscle and the regulation of renin, a key enzyme in the production of ANG II, may bring new insights to the treatment of several diseases, since microvascular rarefaction and arteriolar remodeling are both necessary physiological adaptations that can become maladaptive and lead to target organ damage.

The present study emphasizes the importance of maintaining normal renin regulation as well as ANG II levels during the angiogenesis process with a combination of physiological, genetic, and pharmacological manipulation of the RAS. Understanding the mechanism implied in the angiogenic reaction promoted by ANG II has major therapeutic importance since ACE inhibitors and ANG II receptor blockers have been prescribed for the treatment of a growing number of conditions (25, 32, 45). The genetic variations in- volved in angiogenesis induced by short-term exercise training. Angiogenesis induced by physiological stimuli in adult skeletal muscle and the regulation of renin, a physiological adaptations that can become maladaptive and lead to target organ damage.

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ACKNOWLEDGMENTS

The authors thank Timothy Stodola for expert technical assistance.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute (NHLBI) Grants HL-29587 and HL-82798 and National Institutes of Health-NHLBI Contract N01-HV-28182.

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