C-Reactive Protein Causes Downregulation of Vascular Angiotensin Subtype 2 Receptors and Systolic Hypertension in Mice

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**Background**—Chronic elevations in circulating C-reactive protein (CRP) are associated with a greater risk of hypertension. Whether elevations in CRP cause hypertension is unknown.

**Methods and Results**—Chronic, conscious blood pressure (BP) measurements were performed by radiotelemetry in wild-type CF1 control and CF1 transgenic mice expressing rabbit CRP (CF1-CRP) under the regulation of the phosphoenolpyruvate carboxykinase promoter. Compared with controls, CF1-CRP mice had hypertension that was predominantly systolic, and the severity of hypertension varied in parallel with changes in CRP levels modulated by dietary manipulation. Mice that were hemizygous for the transgene with CRP levels of 9 μg/mL were also hypertensive, indicating that modest elevations in CRP are sufficient to alter BP. CRP transgenic mice had exaggerated BP elevation in response to angiotensin II and a reduction in vascular angiotensin receptor subtype 2 (AT2) expression. In contrast, the decline in BP with angiotensin receptor subtype 1 (AT1) antagonism and vascular AT1 abundance were unaltered, which indicates a selective effect of CRP on AT2. Ex vivo experiments further showed that the CRP-induced decrease in AT2 is a direct effect on the vascular wall, not requiring systemic responses, and that it is reversed by an NO donor, which indicates a role for NO deficiency in the process. In parallel, the chronic inhibition of NO synthase in wild-type mice attenuated vascular AT2 expression without affecting AT1.

**Conclusions**—These findings provide direct evidence for CRP-induced hypertension, and they further identify a novel underlying mechanism involving downregulation of AT2 related to NO deficiency. (*Circulation.* 2007;115:1020-1028.)

**Key Words:** angiotensin ■ C-reactive protein ■ endothelium ■ hypertension ■ nitric oxide ■ receptors

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C-reactive protein (CRP) is an acute-phase reactant that has been shown to be a predictor of the risk of myocardial infarction in apparently healthy individuals. More recently, numerous epidemiological studies have also demonstrated that minor elevations in CRP levels are associated with increased risk of hypertension.1–3 Although such observations implicate a role for CRP in the pathogenesis of hypertension, CRP elevation may instead be the result of vascular injury induced by high blood pressure (BP). Alternatively, elevations in proinflammatory cytokines or acute-phase reactants other than CRP may contribute to the development of hypertension, and the increase in CRP is an epiphenomenon. Thus, it is presently unknown whether CRP directly causes hypertension.
hydrate intake. Along with testing the primary hypothesis, experiments were designed to answer the following questions: (1) Is BP sensitive to both increases and decreases in circulating CRP levels? (2) What is the threshold concentration of circulating CRP in mice that induces hypertension? (3) How does CRP modulate BP?

Methods

Animal Model
Experiments were performed in CF1-CRP mice that express a transgene consisting of the protein-coding region of the rabbit CRP gene linked to the promoter/regulatory region of the rat phosphoenolpyruvate carboxykinase gene. Additional details, including the manipulation of transgene expression by diet, are in the online-only Data Supplement.

Chronic BP Measurements
Chronic, conscious BP measurements were performed by radiotelemetry as described in the online-only Data Supplement. Baseline BP recordings were averaged over a 4-day period on standard chow. The diet was changed to high-carbohydrate chow to dampen transgene expression, and BP was measured over 3 days beginning 4 days after the diet change. The diet was then switched to carbohydrate-free chow to activate transgene expression, and BP was measured over 3 days beginning 4 days after the diet change. To assess BP responses to angiotensin II or norepinephrine, an osmotic minipump (Alzet model 2002; Cupertino, Calif) containing angiotensin II or norepinephrine (Sigma, St Louis, Mo) was implanted in a subcutaneous pocket in the right flank under anesthesia and left in place for 14 days. Angiotensin II was administered at 400 ng/kg per minute, and norepinephrine was given at 1800 ng/kg per minute. To assess the impact of angiotensin receptor subtype 1 (AT₁) antagonism, telmisartan was administered for 7 days at 2 mg/kg per day in the drinking water. As was done with the dietary manipulations, BP responses to angiotensin II, norepinephrine, or telmisartan were averaged over the last 3 days of each treatment.

Plasma Renin Activity
Mouse plasma (8 μL) was incubated at 37°C with and without the addition of an excess of rat angiotensinogen purified from bilaterally nephrectomized rats. Conversion of angiotensin I to angiotensin II was inhibited by the addition of EDTA (0.02 mol/L). Angiotensin II was measured by radioimmunoassay by previously established methods and a commercially available kit (DiaSorin, Stillwater, Minn).

CRP Assays
Circulating levels of rabbit CRP were measured in 10 μL of serum collected by retro-orbital sampling by ELISA as previously described.

Ex Vivo Artery Incubations
Thoracic aortas were harvested and incubated in serum-free, phenol red–free Dulbecco’s modified Eagle’s medium (DMEM) gassed with 95% O₂ for 6 hours at 37°C under sterile conditions. Treatment groups were as follows: DMEM alone (control), DMEM with human recombinant CRP (50 μg/mL), Calbiochem, EMD Biosciences, Inc, San Diego, Calif), and DMEM plus CRP plus S-nitroso-N-acetyl penicillamine (SNAP) (100 μmol/L). Two aortas were pooled per treatment group.

Measurement of AT₁ and AT₂ mRNA Abundance
RNA was isolated from thoracic aortas, and reverse-transcription and real-time polymerase chain reaction was performed for AT₁ and angiotensin receptor subtype 2 (AT₂) as described in the online-only Data Supplement.

Measurement of AT₁ and AT₂ Protein Abundance
AT₁ and AT₂ protein abundance in thoracic aortas was evaluated by immunoblot analysis (see the online-only Data Supplement). Additional experiments were performed with aortas from CF1 mice treated with N′-nitro-L-arginine methyl ester (L-NNAME) in the drinking water at the dose of 100 mg/kg per day for 14 days. This dose of L-NNAME causes an increase in BP in mice to the level equivalent to BP found in endothelial NO synthase–null mice, and such an elevation in BP was confirmed by radiotelemetry in additional instrumented CF1 mice.

Statistical Methods
Results are expressed as mean±SEM. All statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC). Additional details are provided in the online-only Data Supplement. P<0.05 was considered statistically significant.

Results

Effect of CRP on BP
To first determine whether CRP affects BP, we performed chronic BP measurements by radiotelemetry in 12- to 16-week-old male CF1 control versus CF1-CRP mice on standard chow. Whereas CRP levels were <1 μg/mL in CF1 controls, CF1-CRP mice had CRP levels of 45±3 μg/mL. Systolic BP was higher in CF1-CRP mice than in CF1 controls (Figure 1A), diastolic BP was similar (Figure 1B), and pulse pressure (Figure 1C) and mean BP were also higher in CF1-CRP mice than in CF1 controls (122±4 versus 110±1 mm Hg, respectively; P<0.05). In contrast, heart rate and the levels of activity of the mice were similar (Figure 1D, 1E). These findings indicate that CRP causes hypertension in mice and that it is primarily systolic hypertension.

To determine whether BP is sensitive to either declines or elevations in circulating CRP levels, alterations in BP with dietary manipulation of transgene expression were investigated. BP was measured by radiotelemetry over a 4-day period on standard chow, the diet was changed to high-carbohydrate chow to dampen transgene expression, and BP was measured over a 3-day period beginning 4 days after the diet change. The diet was then changed to a carbohydrate-free, protein-rich chow to activate transgene expression, and BP was measured over a 3-day period beginning 4 days after the diet change. Neither systolic nor diastolic BP was altered by the diet changes in CF1 control mice in which CRP levels were <1 μg/mL under all conditions (Figure 2A). In contrast, in CF1-CRP mice, systolic BP fell by 12 mm Hg when CRP was lowered from 45±3 to 19±1 μg/mL by placement on the high-carbohydrate diet, and it rose by 11 mm Hg when CRP levels were then increased to 123±15 μg/mL by placement on the carbohydrate-free diet (Figure 2B). Diastolic BP in CF1-CRP mice remained unchanged when CRP levels were lowered by the high-carbohydrate diet but increased by 9 mm Hg when CRP was elevated by the carbohydrate-free diet. These findings indicate that there are marked alterations in BP, particularly in systolic BP, within days of either declines or elevations in CRP that parallel the changes in CRP.
To gain greater insight into the threshold level of CRP that affects BP in mice, CF1-CRP transgenic mice were mated with CF1 mice, and CRP levels and BP were evaluated in the offspring that were hemizygous for the transgene (designated CF1-CRP-low). When compared with CF1 controls, the CF1-CRP-low mice on either the standard diet with CRP levels of 15±5 μg/mL or the high-carbohydrate diet with CRP levels of 9±4 μg/mL had elevated systolic BP (Figure 2C). In contrast, diastolic BP did not differ between the 3 groups (Figure 2D). Thus, even a modest elevation in CRP, comparable to that observed in otherwise healthy humans without active infection or inflammation,12 is sufficient to induce hypertension in mice. All ensuing studies were performed in CF1-CRP-low mice to evaluate the underlying mechanisms in the setting of minor elevations in CRP.

Effect of CRP on BP Responses to Angiotensin II
To determine the mechanism(s) underlying CRP-induced hypertension, plasma renin concentrations were measured, and BP responses to angiotensin II (400 ng/kg per minute) and norepinephrine (1800 ng/kg per minute) administration via osmotic minipump were compared in CF1 control and CF1-CRP-low mice. Plasma renin activity was not elevated in CF1-CRP-low mice compared with CF1 controls (27.0±2.0 versus 50.9±11.2 ng/mL per hour, respectively; $P>0.05$). Angiotensin II caused a larger increase in systolic BP from baseline in CF1-CRP-low mice than in CF1 controls (30±8 versus 8±4 mm Hg, respectively; $P=0.01$). The percentage increase in systolic BP was also greater in CF1-CRP-low versus CF1 control mice (Figure 3A). Angiotensin II tended to increase diastolic BP to a greater extent in CF1-CRP-low mice than in CF1 controls (25±9 versus 7±2 mm Hg, respectively; $P=0.06$). The percentage increase in diastolic BP with angiotensin II also tended to be greater in CF1-CRP-low mice ($P=0.06$; Figure 3B). In contrast, norepinephrine caused a similar rise in systolic BP and in diastolic BP from baseline in CF1-CRP-low versus CF1 control mice (15±3 versus 15±5 mm Hg for systolic BP and 5±2 versus 8±3 mm Hg for diastolic BP, respectively; $P=NS$). As a result, relative increases in systolic BP and in diastolic BP from baseline with norepinephrine were not affected by CRP status (Figure 3C, 3D). Thus, CRP causes a selective increase in BP sensitivity to angiotensin II.

To determine the basis for the exaggerated BP response to angiotensin II with CRP, we compared changes in BP with the oral administration of the AT1 antagonist telmisartan (2 mg/kg per day) in the CF1-CRP-low and CF1 control mice. Telmisartan caused reductions in systolic BP and diastolic BP in both groups, and the percentage decreases in both systolic and diastolic BP were not affected by CRP status (Figure 3E, 3F). These cumulative in vivo findings reveal that CRP causes a selective increase in BP sensitivity to angiotensin II in the absence of alterations in AT1-mediated responses, suggesting that CRP-induced hypertension is related to an effect on AT2 function.

Effect of CRP on Vascular Angiotensin Receptor Expression
To elucidate the basis for enhanced sensitivity to angiotensin II, vascular angiotensin receptor expression was evaluated in studies of thoracic aortas isolated from CF1 control and CF1-CRP-low mice. Relative abundance of mRNA for the angiotensin receptor subtype 1a (AT1a), subtype 1b (AT1b), and subtype 2 (AT2) was determined by real-time reverse-transcription polymerase chain reaction. Whereas AT1a and
AT1b transcript abundance was similar in the control and CF1-CRP-low groups (Figure 4A, 4B), AT2 mRNA expression was decreased by 98% in the aortas of CF1-CRP-low mice (Figure 4C). In parallel, total AT1 protein expression was similar in the control and CF1-CRP-low groups (Figure 4D, 4E), whereas AT2 protein abundance was decreased by 48% in the aortas of CF1-CRP-low mice (Figure 4F, 4G) (see also Figure I in the online-only Data Supplement). Thus, vascular AT2 expression is downregulated by CRP in vivo.

To determine whether the reduction in AT2 in CF1-CRP-low mice is a direct effect of CRP on the vasculature, ex vivo experiments were performed with thoracic aortas from CF1 mice. Aortas were incubated under control conditions or in the presence of CRP for 6 hours, and angiotensin receptor expression was evaluated. Whereas CRP had no effect on AT1 abundance (Figure 5A, 5B), AT2 abundance was decreased by 74% (Figure 5C, 5D) (see also Figure II in the online-only Data Supplement), which paralleled the in vivo findings (Figure 4D to 4G). CRP that was heat-inactivated by previously described methods13 did not alter AT2 expression (87±17% of control treatment with media alone; n=4; P=0.53), indicating that potential nonprotein components of the CRP preparation, such as sodium azide or endotoxin, do not underlie the ex vivo findings. Thus, CRP directly reduces vascular AT2 receptor expression, and the changes in receptor abundance in vivo are not the consequence of CRP-induced BP elevation or CRP-induced systemic neurohormonal or immune responses.

We recently demonstrated that CRP causes potent inhibition of the activation of endothelial NO synthase in cultured endothelial cells, in mouse arteries studied ex vivo, and in mice in vivo.13 We therefore performed additional ex vivo incubations of aortas to determine whether CRP-induced changes in AT2 abundance are due to declines in bioavailable NO. Whereas AT1 expression remained unaltered (Figure 5A, 5B), concomitant incubation with the NO donor SNAP attenuated the reduction in AT2 caused by CRP (Figure 5C, 5D).

To determine whether NO modulation of vascular AT2 expression also occurs in vivo, CF1 mice were administered the NO synthase antagonist L-NAME (100 mg/kg per day orally) for 2 weeks, and angiotensin receptor expression was...
assessed in the thoracic aorta. Whereas there was no effect of decreasing NO bioavailability on AT1 (Figure 6A, 6B), L-NAME treatment caused a 70% reduction in AT2 protein abundance (Figure 6C, 6D) (see also Figure III in the online-only Data Supplement). These cumulative findings indicate that CRP downregulates vascular AT2 expression and that this is due to a CRP-induced decline in bioavailable NO.

Discussion

Circulating levels of CRP are an independent predictor of the risk of hypertension.1–3 However, the role of CRP in the pathogenesis of hypertension is not known. In the present study we have demonstrated that CRP causes a sustained increase in BP in mice and that it is primarily systolic hypertension. In addition, we have shown that the increase in BP induced by CRP is related to an augmented pressor response to angiotensin II that is associated with a reduction in vascular AT2 expression. These findings provide the first causal linkage between elevations in CRP, the renin–angiotensin system, and hypertension.

In previous studies of CRP and hypertension, the short-term infusion of CRP in mice and humans had no effect on BP.14 However, vehicle and contaminants found in CRP preparations such as endotoxin and sodium azide can have direct effects on vascular cells and can cause vasodilation and hypotension,15–17 and they may have interfered with the potential impact of CRP on BP. Other experiments performed in CRP transgenic mice on an apolipoprotein E–null background revealed no effect of CRP on BP.18 Variability in intermittent BP measurements with the tail-cuff technique and stress imposed on the animals by restraint may have limited the ability to detect differences in BP in this study.19,20 The present investigation has the advantages that CRP levels were regulated by a transgene such that possible complicating variables introduced by the short-term administration of CRP preparations were avoided and that BP was measured chronically and continuously in a large number of unrestrained mice with the use of radio transmitters.

In addition to demonstrating systolic hypertension in CF1-CRP transgenic mice on standard chow, we showed that fluctuation in CRP levels obtained by modifying transgene activation via changes in dietary carbohydrate content resulted in parallel alterations in BP. Because the identical dietary manipulations had no effect on BP in CF1 control mice lacking the transgene, the alterations in BP were due to CRP and not other factors. With a coefficient of variation of 1.3% for systolic BP in CF1-CRP mice on the initial standard diet, the reduction in systolic BP of 12 mm Hg (or 6%) after conversion to a high-carbohydrate diet is not likely explained by spontaneous variation in BP or carryover effect of the initial diet and CRP levels. The comparable rise in systolic BP of 11 mm Hg (or 6%) on switching from a high-carbohydrate to a carbohydrate-free diet is also unlikely to be due to carryover because it is an absolute reversal of the prior fall in BP on placement on a high-carbohydrate diet. Further studies of hemizygous transgenic mice (CF1-CRP-low) indicated that elevated BP occurs in mice with CRP levels in the range of 9 µg/mL. In addition, the “dose response” of systolic BP to CRP that was observed with concentrations of <1 versus 9 versus 15 µg/mL suggests that systolic BP would likely be elevated above normal with CRP levels of ≥3 µg/mL, which represents the high-risk range for CRP.12 These cumulative findings indicate that BP modulation by CRP occurs over a period of days, that CRP-induced hypertension can be reversed if CRP levels are lowered, and that it occurs at modest plasma concentrations that are comparable to those observed in otherwise healthy humans without known acute inflammation or infection.12

In studies aimed at elucidating the mechanisms by which CRP increases BP, a selective increase in BP sensitivity to angiotensin II was demonstrated in the CRP transgenic mice. However, AT1 antagonism with telmisartan yielded comparable declines in BP in transgenic and control mice, indicating that the exaggerated sensitivity to angiotensin II in the former is not mediated by AT1. In parallel experiments, vascular AT1 expression was not altered by CRP, whereas both mRNA and protein abundance for AT2 were diminished. These findings...
contrast with those of previous studies limited to cultured vascular smooth muscle cells that indicated that CRP upregulates AT1.21 However, the present observations in freshly isolated aortas are more likely to represent receptor status in vivo because vascular smooth muscle cell phenotype can change in culture.22 Although not observed in all prior studies of genetic knockdown of AT2, the loss of AT2 has been found to cause an elevation in basal BP in both mice and rats.23–25 In Sprague-Dawley rats in which AT2 knockdown was accomplished by administering AT2 antisense cDNA in the neonatal period, primarily basal systolic BP was increased during adulthood.23 Mice and rats with AT2 deficiency have uniformly exhibited exaggerated increases in BP in response to angiotensin II infusion,23–25 whereas the BP response to AT1 blockade in mice with AT2 deficiency is identical to that of wild-type mice.23 Thus, multiple characteristics of the hypertension phenotype of the CRP transgenic mice mimic those of genetic AT2 deficiency. When combined with our finding of CRP-induced vascular AT2 downregulation, these observations suggest that the hypertension in the CRP trans-
genic mice is explained by the reduction in vascular AT2. In addition to blunting vasoconstrictor response to angiotensin II, AT2 receptors protect against hypertension by inhibiting renin synthesis and angiotensin II production in the kidneys. However, elevated renin and angiotensin are not likely to contribute to the hypertension in the CRP transgenic mice because plasma renin concentrations were similar to those in controls. As such, the primary defect is likely the reduction in vascular AT2.

In parallel with our finding that CRP induces primarily systolic hypertension and increased pulse pressure in mice, in certain epidemiological studies CRP levels have been associated specifically with elevated pulse pressure and systolic BP. The mechanism(s) by which the observed changes in AT2 induced by CRP lead to systolic hypertension in our study is yet to be elucidated. An accelerated age-related decline in aortic distensibility has been implicated in the pathogenesis of isolated systolic hypertension, which is the most common subtype of hypertension in humans after the age of 50 years, and CRP levels increase gradually with aging in humans. One recent study in rats indicated that the stimulation of AT2 decreases vascular stiffness by increasing elastin deposition in the vascular wall. Whether the reduction in aortic AT2 in the CRP transgenic mice results in a loss of elastic tissue and impaired aortic distensibility or whether there is greater angiotensin II–related vascular remodeling in resistance arteries remains to be evaluated. In addition, because the AT1 receptor also modulates BP by actions in the adrenal gland and central nervous system, further investigations of nonvascular mechanisms in CF1-CRP mice are now warranted.

**Figure 5.** CRP downregulates vascular AT2 expression ex vivo by decreasing NO bioavailability. Thoracic aortas from CF1 mice were incubated ex vivo for 6 hours under control conditions or in the presence of CRP with and without the addition of the NO donor SNAP. A, Relative abundance of AT1 protein was evaluated by immunoblot analysis. B, Cumulative results are shown for AT1 protein in 6 independent experiments. C, Relative abundance of AT2 protein was evaluated by immunoblot analysis. D, Cumulative results are shown for AT2 protein in 6 independent experiments. In B and D, receptor abundance is expressed normalized to actin, and values are mean±SEM. *P<0.05 vs control; †P<0.05 vs CRP alone.

**Figure 6.** NO modulates vascular AT2 in vivo. CF1 mice were administered drinking water or drinking water containing the NO synthase antagonist L-NAME for 14 days, and thoracic aortas were harvested. A, Relative abundance of AT1 protein was evaluated by immunoblot analysis. B, Cumulative results are shown for AT1 protein in 5 independent experiments. C, Relative abundance of AT2 protein was evaluated by immunoblot analysis. D, Cumulative results are shown for AT2 protein in 5 independent experiments. In B and D, receptor abundance is normalized relative to actin, and values are mean±SEM. *P<0.05 vs control.
Along with the experiments demonstrating CRP-mediated downregulation of vascular AT2, in vivo, studies were performed to determine the underlying mechanism(s). It is more likely that the loss of vascular AT2 is a primary event and not secondary to the hypertension because studies of distal aortic banding in rats indicate that pressure overload increases AT2 expression in the thoracic aorta.36 We performed ex vivo incubations of mouse thoracic aortas with recombinant human CRP, which has characteristics very similar to those of rabbit CRP based on both in vivo and in vitro studies. Both are acute-phase reactants in their species, they rise and then fall after an inflammatory stimulus in a similar manner and at comparable concentrations, they activate complement and bind to phosphocholine, and their binding characteristics and the structural features underlying their binding characteristics are shared.37 In the ex vivo experiments, CRP caused AT2 downregulation, whereas AT1 expression was unaltered, paralleling the in vivo findings. These results indicate that systemic processes, including immune response mechanisms such as complement activation, are not required for CRP modulation of vascular AT2. Alternatively, the effect of CRP on AT2 occurs via direct action(s) on vascular cells. Further ex vivo experiments showed that the NO donor SNAP blunted the CRP-induced AT2 downregulation. In parallel, NO-related modulation of vascular AT2 was demonstrated in vivo in the studies in which NO synthase antagonism in wild-type mice caused a selective loss of vascular AT2. When considered along with our prior observation that CRP inhibits the activation of endothelial NO synthase in cultured endothelial cells, in arteries studied ex vivo, and in vivo in mice,13 these findings indicate that CRP downregulation of vascular AT2 expression is due to a CRP-induced decline in bioavailable NO. Although previous work investigating AT2 expression in PC12 cells has demonstrated positive modulation of the receptor by NO-mediated mechanisms,38 the molecular basis of regulation of AT2 gene expression by NO is unknown, and detailed, focused studies are now required to elucidate the underlying processes.

The present observations provide the first direct evidence for hypertensive action of CRP, and they identify a novel series of mechanisms by which CRP induces hypertension by causing NO-sensitive downregulation of vascular AT2. In doing so, our findings provide important new perspectives on the processes by which a byproduct of chronic inflammation has a direct negative impact on cardiovascular health. In addition, we have identified a new model for isolated systolic hypertension. It is anticipated that further research in this realm will enable our basic understanding of hypertension associated with inflammation and aging.

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Disclosures
Dr Shaul reports having received honoraria for participation in a scientific meeting at which data in this article were discussed. The remaining authors report no conflicts.

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We propose that the modulation of these mechanisms may ultimately be used to combat certain forms of hypertension. For isolated systolic hypertension, which is the most common form of hypertension in humans after the age of 50 years, obesity, and aging to NO and renin–angiotensin regulation of blood pressure. In addition, we have identified a new model of CRP, and they reveal a novel series of mechanisms linking a circulating factor that rises with chronic inflammation, by a CRP-related decline in bioavailable NO. These observations provide the first direct evidence for hypertensive action that is a direct effect on the vascular wall, not requiring systemic actions of CRP, and further studies suggest that this is caused predominantly systolic. We further find that blood pressure modulation by CRP occurs over a period of days, that the investigation, we demonstrate that mice expressing a regulatable transgene for CRP have hypertension that is associated with a greater risk of hypertension. Whether elevations in CRP cause hypertension is unknown. In this CLINICAL PERSPECTIVE

Numerous epidemiological studies have demonstrated that chronic elevations in circulating C-reactive protein (CRP) are associated with a greater risk of hypertension. Whether elevations in CRP cause hypertension is unknown. In this investigation, we demonstrate that mice expressing a regulatable transgene for CRP have hypertension that is predominantly systolic. We further find that blood pressure modulation by CRP occurs over a period of days, that the hypertension can be reversed if CRP levels are lowered, and that it occurs at modest levels of CRP that can be observed in otherwise healthy individuals without acute inflammation or infection. The underlying mechanism entails exaggerated responsiveness to angiotensin II that is associated with a reduction in vascular expression of the counterregulatory angiotensin receptor subtype 2. Ex vivo experiments show that the CRP-induced decrease in angiotensin receptor subtype 2 is a direct effect on the vascular wall, not requiring systemic actions of CRP, and further studies suggest that this is caused by a CRP-related decline in bioavailable NO. These observations provide the first direct evidence for hypertensive action of CRP, and they reveal a novel series of mechanisms linking a circulating factor that rises with chronic inflammation, obesity, and aging to NO and renin–angiotensin regulation of blood pressure. In addition, we have identified a new model for isolated systolic hypertension, which is the most common form of hypertension in humans after the age of 50 years. We propose that the modulation of these mechanisms may ultimately be used to combat certain forms of hypertension.
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