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IgG Receptor Fc γ RIIB Plays a Key Role in Obesity-Induced Hypertension

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Abstract

There is a well-recognized association between obesity, inflammation, and hypertension. Why obesity causes hypertension is poorly understood. We previously demonstrated using a C-reactive protein (CRP) transgenic mouse that CRP induces hypertension that is related to NO deficiency. Our prior work in cultured endothelial cells identified the Fc γ receptor IIB (Fc γ RIIB) as the receptor for CRP whereby it antagonizes endothelial NO synthase. Recognizing known associations between CRP and obesity and hypertension in humans, in the present study we tested the hypothesis that Fc γ RIIB plays a role in obesity-induced hypertension in mice. Using radiotelemetry, we first demonstrated that the hypertension observed in transgenic mouse-CRP is mediated by the receptor, indicating that Fc γ RIIB is capable of modifying blood pressure. We then discovered in a model of diet-induced obesity yielding equal adiposity in all study groups that whereas Fc γ RIIB^{+/+} mice developed obesity-induced hypertension, Fc γ RIIB^{-/-} mice were fully protected. Levels of CRP, the related pentraxin serum amyloid P component which is the CRP-equivalent in mice, and total IgG were unaltered by diet-induced obesity; Fc γ RIIB expression in endothelium was also unchanged. However, whereas IgG isolated from chow-fed mice had no effect, IgG from high-fat diet-fed mice inhibited endothelial NO synthase in cultured endothelial cells, and this was an Fc γ RIIB-dependent process. Thus, we have identified a novel role for Fc γ RIIB in the pathogenesis of obesity-induced hypertension, independent of processes regulating adiposity, and it may entail an IgG-induced attenuation of endothelial NO synthase function. Approaches targeting Fc γ RIIB may potentially offer new means to treat hypertension in obese individuals.

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Disclosures

None.

Keywords

C-reactive protein; hypertension; IgG; inflammation; obesity; serum amyloid P component

There is a well-recognized association between obesity, inflammation, and cardiovascular disease.¹ In particular, obesity is a major risk factor for hypertension,^{2,3} and up to four fifths of the 20% increase in the prevalence of hypertension between 1988 to 1994 and 1994 to 2004 in the National Health and Nutrition Examination Surveys have been attributed to increasing body mass index.² Regrettably current approaches to combat the underlying obesity, which focus on nutrition and exercise to achieve weight loss and maintenance, have not been effective in the long term.⁴ In addition, obesity is a risk factor for the development of hypertension that is resistant to single agent therapy.⁵ As such, new therapeutic approaches are needed for the treatment of hypertension in obese individuals.

Circulating levels of the pentraxin C-reactive protein (CRP), which are often interpreted to indicate the presence of low-grade systemic inflammation, are elevated in obese populations including children, adolescents, and young adults.^{6,7} Chronic modest elevations in circulating CRP levels are associated with an increased risk of developing hypertension,⁸ though its direct causal role in human hypertension is unclear.⁹ We previously demonstrated in studies using a CRP transgenic mouse (TG-CRP), allowing overexpression of the pentraxin, that serum concentrations of CRP comparable with those observed with low-grade systemic inflammation in humans induce hypertension.¹⁰ In that work, we further showed that the CRP-induced hypertension is because of the downregulation of endothelial NO synthase (eNOS) activity in vascular endothelial cells,¹⁰ and impaired endothelial function is an important contributing factor to the development of hypertension in humans.¹¹ In studies of cultured endothelial cells and endothelial repair and carotid vascular conductance in vivo in mice, we have determined that endothelial actions of CRP are mediated by the IgG receptor Fc γ receptor IIB (Fc γ RIIB),¹²⁻¹⁴ which we have demonstrated is expressed in endothelial cells.^{14,15} Known ligands for Fc γ RIIB are CRP, the highly homologous pentraxin serum amyloid P component (SAP), which is the acute phase reactant equivalent of CRP in mice,^{16,17} and IgG, which all bind to identical residues in the extracellular domain of the receptor.¹⁸

The present studies using mouse models were designed to better understand the pathogenesis of the hypertension that complicates obesity. Recognizing the associations between CRP and obesity and hypertension, and knowing that Fc γ RIIB is a biologically relevant CRP receptor, we tested the hypothesis that Fc γ RIIB mediates obesity-induced hypertension. We first demonstrated that the hypertension caused by elevations in the known Fc γ RIIB ligand CRP requires the receptor, indicating that Fc γ RIIB is capable of modifying blood pressure (BP). We then discovered in a model of diet-induced obesity, which yielded equal weight gain and equal increase in body fat with high-fat diet (HFD) feeding in all study groups, that whereas Fc γ RIIB^{+/+} mice developed obesity-induced hypertension, Fc γ RIIB^{-/-} mice were fully protected from hypertension. Thus, independent of any effects on body weight or body composition, Fc γ RIIB plays a key role in obesity-induced hypertension.

Methods

Detailed methods are available in the online-only Data Supplement.

Animal Models

To study CRP-induced hypertension and Fc γ RIIB, TG-CRP were crossed with Fc γ RIIB^{-/-} mice to yield Fc γ RIIB^{+/+}, Fc γ RIIB^{+/+};TG-CRP, Fc γ RIIB^{-/-}, and Fc γ RIIB^{-/-};TG-CRP littermates. All mice were fed standard rodent chow.

To study obesity-induced hypertension, Fc γ RIIB^{+/+} and Fc γ RIIB^{-/-} mice were placed on either control diet (CON) or HFD. Mice were maintained on their respective diet for a minimum of 12 weeks. This resulted in 4 experimental groups: (1) Fc γ RIIB^{+/+} CON, (2) Fc γ RIIB^{+/+} HFD, (3) Fc γ RIIB^{-/-} CON, and (4) Fc γ RIIB^{-/-} HFD. Their care and use were approved by the Institutional Animal Care and Use Committees at Baylor College of Medicine and the University of Texas Southwestern Medical Center.

Body Composition

Body composition was measured by dual-energy x-ray absorptiometry.

BP Measurements

Mice underwent tail-cuff BP measurement for 5 consecutive days, using the mean of the last 10 readings on day 5. For radiotelemetry, mice were anesthetized and instrumented with a radiotelemetry device. Mice were allowed to recover until a return of circadian variation in BP and activity were observed. In the CON chow versus HFD experiments, mice were maintained on their respective study diet throughout the radiotelemetry measurements.

Serum CRP, SAP, and IgG

Serum CRP, SAP, and total IgG were quantified by ELISA.

Fc γ RIIB Expression

Primary aortic endothelial cells were obtained by collagen digestion, and spleens were harvested and splenic cells dispersed by sieving. Cells then underwent fluorescence-activated cell sorting analysis using monoclonal antibody to Fc γ RIIB (anti-CD16/32b, 2.4G2) and anti-CD31 (PECAM-1 [platelet-endothelial cell adhesion molecule 1]) or anti-CD45R(B220) antibodies for endothelial cell or B-cell selection, respectively.

NO Synthase Activity in Cultured Endothelial Cells

Total IgG was isolated from wild-type mice after 12 weeks of CON versus HFD feeding. Bovine aortic endothelial cells were incubated with either CON IgG or HFD IgG, and NO synthase activation by vascular endothelial growth factor was then evaluated by measuring ¹⁴C-L-arginine conversion to ¹⁴C-L-citrulline. Additional experiments were performed in bovine aortic endothelial cell transfected with control small interfering RNA or small interfering RNA targeting Fc γ RIIB.

Statistical Analysis

Statistical analysis for animal experiments was performed using 2-way ANOVA to interrogate the effects of genotype (Fc γ RIIB^{+/+} versus Fc γ RIIB^{-/-}) and CRP (wild-type versus TG-CRP) or diet (CON versus HFD) and the interaction effect. For endothelial cell culture experiments, 1-way ANOVA was used with Student–Newman–Keuls post-test analysis. Differences were considered significant at $P < 0.05$.

Results

CRP, Fc γ RIIB, and BP

We previously demonstrated that modest elevations in CRP causes hypertension in mice.¹⁰ However, the receptor mediating the hypertension invoked by CRP is unknown, and whether Fc γ RIIB affects BP is unknown. Radiotelemetry measurements of systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were performed in conscious unrestrained mice to determine whether Fc γ RIIB is necessary for CRP-induced hypertension. In Fc γ RIIB^{+/+};TG-CRP mice, SBP and DBP and MAP were all elevated compared with mice not expressing the CRP transgene. CRP caused the mean SBP to increase from 123 to 133 mm Hg, mean DBP rose from 92 to 100 mm Hg, and mean MAP increased from 108 to 117 mm Hg (Figure 1A–1C). In contrast, SBP, DBP, and MAP were not elevated by CRP in Fc γ RIIB^{-/-} mice. Heart rate was increased in TG-CRP compared with non-TG-CRP mice (Figure 1D); there was no difference in heart rate related to the presence versus absence of Fc γ RIIB. These findings reveal that Fc γ RIIB is required for CRP to cause hypertension in mice.

Diet-Induced Obesity Model

Having demonstrated in the TG-CRP mice that Fc γ RIIB is capable of participation in the pathogenesis of hypertension, we next wished to determine whether the receptor contributes to the disorder in a clinically relevant chronic condition that is commonly complicated by hypertension. Because obesity is a well-recognized risk factor for hypertension in humans^{2,3} and mice placed on HFD develop hypertension,^{19,20} we evaluated the possible role of Fc γ RIIB in hypertension caused by diet-induced obesity in mice. To accomplish this, starting at 5 to 6 weeks of age Fc γ RIIB^{+/+} or Fc γ RIIB^{-/-} mice were placed on either CON or HFD diet. Beginning 2 weeks after the initiation of the diets, predictably the mice on HFD had greater body weight than the mice on CON diet, and the difference was maintained throughout the 12-week period on the diet (Figure 2A). At 2 and 4 weeks on the diets there was a small difference in weight between HFD-fed Fc γ RIIB^{+/+} mice and HFD-fed Fc γ RIIB^{-/-} mice, with the former weighing slightly more than the latter. However, the difference did not persist >4 weeks on diet.

Body composition was assessed by dual-energy x-ray absorptiometry after 12 weeks of CON or HFD feeding. HFD-fed Fc γ RIIB^{+/+} mice and HFD-fed Fc γ RIIB^{-/-} mice had body weights that were comparable and increased by 35% above the body weights of mice on CON. The vast majority of the increase in body weight was attributed to an increase in adiposity (Figure 2B), with both Fc γ RIIB^{+/+} and Fc γ RIIB^{-/-} mice displaying a 50% increase in percent body fat on HFD (Figure 2C). Importantly, the adiposity that resulted from HFD

feeding was equal in Fc γ RIIB^{+/+} and Fc γ RIIB^{-/-} mice (Figure 2B and 2C), indicating that the presence versus absence of the receptor does not affect body composition.

Fc γ RIIB and HFD-Induced Hypertension

Tail-cuff BP measurements were first used to assess whether the presence or absence of Fc γ RIIB affects BP under standard conditions and also the potential role of Fc γ RIIB in HFD-induced hypertension. Tail-cuff measurements can be used to accurately evaluate SBP in conscious, unanesthetized mice.²¹ SBP was similar in control chow (CON)-fed Fc γ RIIB^{+/+} and Fc γ RIIB^{-/-} mice (Figure 3A). In Fc γ RIIB^{+/+} mice, SBP was 10 mm Hg greater in HFD-fed versus CON-fed mice. The increase in SBP was similar in degree to that previously reported in HFD-fed versus CON-fed mice.^{19,20} In contrast, in Fc γ RIIB^{-/-} mice, SBP was similar in HFD-fed and CON-fed animals.

To confirm the findings for SBP obtained by tail cuff, and to also evaluate DBP, which is not accurately evaluated by cuff devices,²² further experiments were performed using radiotelemetry. SBP by radiotelemetry was increased by 13 mm Hg in HFD-fed compared with CON-fed Fc γ RIIB^{+/+} mice, but statistical significance was not achieved ($P=0.06$ for diet in 2-way analysis; Figure 3B). In contrast, diet-induced obesity did not alter SBP in Fc γ RIIB^{-/-} mice. Diastolic BP was elevated 9 mm Hg by HFD in Fc γ RIIB^{+/+} mice but not in Fc γ RIIB^{-/-} mice ($P<0.05$ for interaction in 2-way ANOVA; Figure 3C). MAP in the 4 experimental groups displayed the same pattern, increased 11 mm Hg by HFD in wild-type mice but not in receptor null mice ($P<0.05$ for interaction; Figure 3D). Heart rate was significantly increased by HFD (HFD versus CON; $P<0.05$; 2-way ANOVA), but there was no effect of genotype ($P>0.05$; Figure 3E).

Additional analyses were performed to determine whether the impact of diet-induced obesity on BP, or the impact of Fc γ RIIB genotype on the BP response to obesity, occurs primarily during daytime or during nighttime, which represent periods of low versus high activity, respectively. Figure 4 shows the measurements during light hours (open bars) and dark hours (filled bars). In all comparisons, BP was increased at night compared with day as expected. SBP was increased during the day in Fc γ RIIB^{+/+} HFD-fed mice (Figure 4A), and in contrast there was no impact of HFD on SBP in Fc γ RIIB^{-/-} mice, either during daytime or during nighttime. Diastolic BP and MAP (Figure 4B and 4C) were raised by HFD in Fc γ RIIB^{+/+} mice both during daytime and during nighttime, whereas diet had no effect on either of those parameters during either 12-hour period in Fc γ RIIB^{-/-} mice. Therefore, increased BP caused by HFD is not related to a change in the diurnal BP pattern, and the presence versus absence of Fc γ RIIB influences obesity-induced hypertension equally throughout the 24-hour day. Activity monitoring confirmed day-night variation in activity in the 4 experimental groups (Figure 4D). There was a trend for mice on HFD to be less active at night compared with CON-fed mice ($P=0.06$). Collectively these findings reveal that Fc γ RIIB participates in the pathogenesis of the hypertension that accompanies diet-induced obesity.

Diet-Induced Obesity and Fc γ RIIB Ligands

The known ligands for Fc γ RIIB are the pentraxins CRP and SAP and the Fc region of IgG, which have shared binding sites on Fc receptors.¹⁸ Seeking to identify the Fc γ RIIB ligand that is responsible for HFD-induced hypertension and recognizing that obesity is a chronic inflammatory state, we hypothesized that 1 of these mediators of inflammatory response is elevated in the setting of HFD feeding and resulting obesity in mice. Analyzing serum from Fc γ RIIB^{+/+} mice fed CON versus HFD for 12 weeks, we found that there was no change in serum CRP in response to HFD feeding and the obesity that it causes (Figure 5A). CRP was surprisingly lower in HFD-fed versus CON-fed Fc γ RIIB^{-/-} mice. Serum SAP also did not change in response to HFD in Fc γ RIIB^{+/+} mice (Figure 5B). However, serum SAP rose modestly with HFD feeding in Fc γ RIIB^{-/-} mice. Total IgG additionally was similar in CON-fed versus HFD-fed Fc γ RIIB^{+/+} mice (Figure 5C). Likely related to the lack of the inhibitory Fc receptor in B cells in the Fc γ RIIB^{-/-} mice, the null mice had marked elevations in total IgG compared with wild-type mice; however, the elevations in total IgG in Fc γ RIIB^{-/-} were similar in CON-fed versus HFD-fed mice. Thus, there is not a demonstrable change in the circulating level of a known Fc γ receptor ligand in the setting of HFD feeding and resulting obesity in mice.

Fc γ RIIB Expression

Possible effects of HFD on receptor expression were evaluated by fluorescence-activated cell sorting analysis in endothelial cells, in which we previously demonstrated their activation antagonizes eNOS,¹⁴ and in B cells in which Fc γ RIIB attenuates B-cell receptor-mediated processes.²³ In both endothelial cells and B cells, Fc γ RIIB expression was similar in cells obtained from CON versus HFD-fed mice (Figure S1 in the online-only Data Supplement). Thus, diet-induced obesity does not affect Fc γ RIIB expression, particularly in endothelium in which the receptor is known to alter vascular function.

Endothelial Actions of IgG

Observing that circulating levels of CRP, SAP, and IgG, and also Fc γ RIIB expression were not altered by HFD feeding, possible changes in IgG function were evaluated by studying IgG effects on eNOS in cultured endothelial cells. Treatment with IgG from CON-fed mice did not alter vascular endothelial growth factor activation of eNOS; in contrast, HFD IgG caused marked attenuation of eNOS activation (Figure 6A). To determine whether the actions of HFD IgG are mediated by Fc γ RIIB, the receptor was silenced by small interfering RNA (Figure 6B). Whereas HFD IgG blunted eNOS activation in control small interfering RNA-transfected cells, it had no effect in Fc γ RIIB-depleted endothelial cells (Figure 6C). Thus, diet-induced obesity yields IgG that antagonizes eNOS via Fc γ RIIB.

Discussion

Seeking to better understand the basis for obesity-induced hypertension, we designed experiments in mice to determine the role of Fc γ RIIB in the pathogenesis of the disorder. First testing whether a known ligand for Fc γ RIIB alters BP via the receptor, we demonstrated that CRP-induced hypertension in the mouse is fully dependent on Fc γ RIIB. We then discovered in a model of diet-induced obesity with equal increases in body weight

and body fat in wild-type and null mice that whereas obese Fc γ RIIB^{+/+} mice developed hypertension, obese Fc γ RIIB^{-/-} mice were fully protected from hypertension. These observations indicate that independent of any effect on body weight or body composition, Fc γ RIIB plays a key role in obesity-induced hypertension.

The basis for the CRP-induced hypertension that we now show is mediated by Fc γ RIIB was elucidated in our previous studies.¹⁰ TG-CRP mice displayed exaggerated BP elevation in response to angiotensin II and a reduction in vascular angiotensin II receptor subtype 2 expression. In contrast, the decline in BP with angiotensin receptor subtype 1 antagonism and vascular angiotensin receptor subtype 1 abundance were unaltered in the TG-CRP mice, indicating a selective effect of CRP on vascular angiotensin II receptor subtype 2. Additional experiments showed that the CRP-induced decrease in vascular angiotensin II receptor subtype 2 is caused by NO deficiency, and earlier studies indicated that NO deficiency results from potent antagonism of eNOS by the CRP-Fc γ RIIB tandem.¹⁴ The eNOS antagonism by CRP entails the coupling of Fc γ RI to Fc γ RIIB by Src kinase, and the activation of SH2 domain-containing inositol 5'-phosphatase 1, which attenuates signaling downstream of PI3 kinase, thereby preventing Akt activating phosphorylation at Ser473.^{12,13} Thus, we now know that Fc γ RIIB activation by CRP initiates a series of alterations in intracellular signaling in endothelial cells, and that the actions of the pentraxin-receptor pair ultimately cause hypertension in mice.

Along with an important role for endothelial dysfunction,²⁴ altered sympathetic nervous system activity may participate in obesity-related hypertension.²⁵ Interestingly, we observed that heart rate is increased in TG-CRP mice and in HFD-fed obese mice, and that whereas Fc γ RIIB deletion normalizes BP in the setting of either CRP elevation or diet-induced obesity, it has modest, if any, effect on the heart rate elevation. The finding that Fc γ RIIB participates in the hypertension but not in the tachycardia observed with raised CRP or obesity, with the heart rate changes likely mediated by sympathetic nervous system activation,²⁵ suggests a peripheral (non-CNS, non-sympathetic nervous system) site of action of Fc γ RIIB. As such, the distinct impact of the receptor on BP versus heart rate is consistent with a role in hypertension for Fc γ RIIB in endothelium, which is the cell type implicated in our prior studies of the vascular mechanisms of action of CRP.¹²⁻¹⁴

Observing the parallel requirement for Fc γ RIIB in CRP- and obesity-induced hypertension, we were then prompted to identify the Fc γ RIIB ligand that is operative in the obesity-induced disorder. In wild-type mice we found that there is no change in serum CRP in response to HFD feeding and the obesity that it causes. This is consistent with prior reports that CRP is not elevated in mice in response to a HFD.^{26,27} Recognizing that the acute phase reactant in mice is the highly homologous pentraxin SAP,¹⁶ we also assessed whether SAP is altered by HFD in wild-type mice, and found that it is unaffected. Surprisingly, SAP was modestly increased in Fc γ RIIB^{-/-} mice on HFD. However, SAP levels in healthy mice are between 25 and 60 μ g/mL and during an acute inflammatory reaction they reach 250 μ g/mL,^{16,28} and the highest SAP concentration observed in HFD-fed Fc γ RIIB^{-/-} was only 55 μ g/mL. Because neither CRP nor SAP levels were elevated by HFD in association with the hypertension that HFD invokes in wild-type mice, we determined serum concentrations of total IgG as it is also a ligand for Fc γ RIIB. HFD did not affect total IgG in wild-type mice,

and predictably total IgG was increased in Fc γ RIIB^{-/-} mice because the receptor is expressed in B cells in which it negatively regulates IgG production.²⁹ In mice others have observed either no effect of HFD on IgG or an increase in total IgG.^{30,31} In humans, total IgG may rise with obesity,³² and it falls after weight loss after gastric banding.³³ We additionally evaluated possible effects of HFD on Fc γ RIIB abundance, and found that expression in both endothelial cells, where the receptor alters vascular function, and B cells was not modified by HFD feeding. Alternatively, we discovered that the IgG obtained from HFD-fed mice potently antagonizes eNOS activation, and furthermore that the eNOS antagonism is entirely Fc γ RIIB dependent. These findings mirror those we previously made on the role of the receptor in eNOS antagonism by CRP,¹² and they are consistent with the prior observation that aortic endothelial cells isolated from HFD-fed mice display decreased activating phosphorylation of eNOS at Ser1176 compared with endothelial cells from control diet-fed mice.²⁴ The particular nature of the IgG generated during diet-induced obesity that antagonizes eNOS can now be interrogated in future studies. One possibility is that the culprit is IgG autoantibodies, which increase with obesity and are thought to link obesity with autoimmune disorders.³¹

Obesity-related hypertension is a perplexing clinical problem, and efforts to combat the underlying obesity regrettably can often be unsuccessful. We have discovered Fc γ RIIB as a new mediator of obesity-induced hypertension that participates in the disorder in mechanisms that are unrelated to the control of body weight or body composition. Novel therapeutic approaches targeting Fc γ RIIB-related processes may offer valuable new means to combat obesity-related hypertension independent of strategies to promote weight loss.

Perspectives

The mechanisms that link obesity and hypertension are incompletely understood. The mainstay of clinical management for obesity-related conditions is to encourage weight loss. However, such efforts are often unsuccessful and therapies that complement weight loss regimens would be useful. Having discovered that Fc γ RIIB is critically involved in obesity-induced hypertension, approaches targeting Fc γ RIIB may offer potentially new means to treat hypertension in obese individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

- We demonstrate a novel role for the inflammatory receptor, Fc γ receptor IIB (Fc γ RIIB), in obesity-induced hypertension.

What Is Relevant?

- The mainstay of clinical management for obesity-related conditions is to encourage weight loss. However, such efforts are often unsuccessful and therapies that complement weight loss regimens would be useful. Having discovered that Fc γ RIIB plays an important role in obesity-induced hypertension, approaches targeting Fc γ RIIB may offer potentially new means to treat hypertension in obese individuals.

Summary

We have discovered Fc γ RIIB participates in the development of obesity-induced hypertension by mechanisms that are unrelated to adiposity. Therefore, novel therapeutic approaches targeting Fc γ RIIB-related processes may offer valuable new means to combat obesity-related hypertension independent of strategies to promote weight loss.

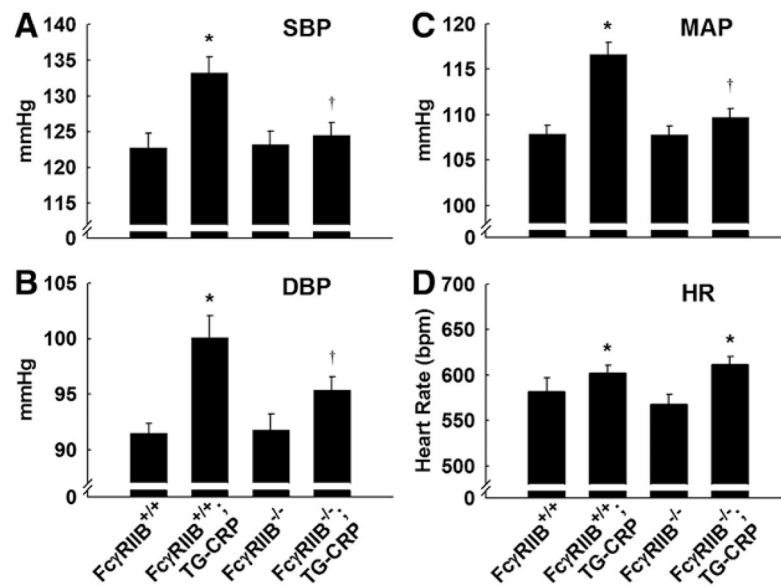


Figure 1.

Fcγ receptor IIB (FcγRIIB) is required for C-reactive protein (CRP)-induced systolic and diastolic hypertension. Systolic blood pressure (SBP; **A**), diastolic blood pressure (DBP; **B**), mean arterial pressure (MAP; **C**), and heart rate (HR; **D**) were measured by radiotelemetry in conscious FcγRIIB^{+/+} control, FcγRIIB^{+/+};transgenic mouse (TG)-CRP, FcγRIIB^{-/-} control and FcγRIIB^{-/-};TG-CRP male littermates. Values are mean±SEM (n=8–10). In 2-way ANOVA analysis, SBP, DBP, MAP, and HR were significant for the effect of CRP ($P<0.05$). Furthermore, SBP and MAP had a significant interaction of the main effects ($P<0.05$). The effect of genotype was not significant in any comparison ($P>0.05$). In post-test analysis * $P<0.05$ vs control, † $P<0.05$ vs FcγRIIB^{+/+}.

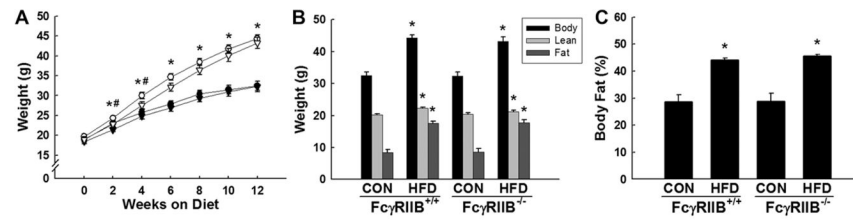


Figure 2.

Fcγ receptor IIB (FcγRIIB)^{+/+} and FcγRIIB^{-/-} mice gain equal weight and fat mass on high-fat diet (HFD). At 5 to 6 weeks of age, FcγRIIB^{+/+} and FcγRIIB^{-/-} male mice were placed on either a control chow diet (CON) or a HFD. **A**, Body weight was measured over time in FcγRIIB^{+/+} CON (●), FcγRIIB^{+/+} HFD (○), FcγRIIB^{-/-} CON (▼), and FcγRIIB^{-/-} HFD (▽). **B** and **C**, After 12 weeks on the respective diets, body weight was measured and lean body mass and fat mass were measured by dual-energy x-ray absorptiometry (DEXA; **B**), and percentage body fat was calculated (**C**). Values are mean±SEM (n=8–12), *P<0.05 vs CON diet, #P<0.05 vs FcγRIIB^{-/-} HFD.

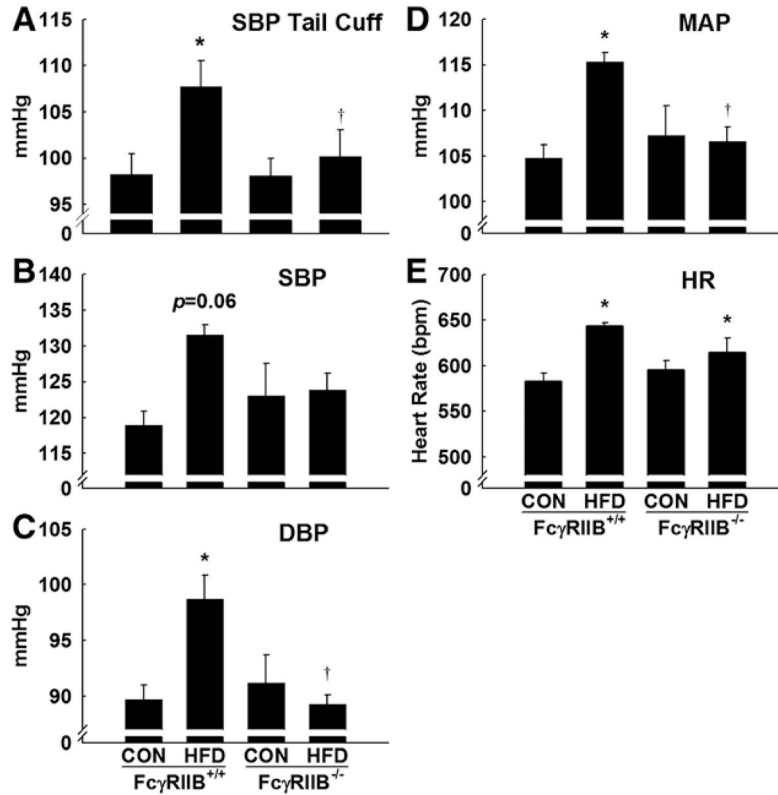


Figure 3.

Fc γ receptor IIB (Fc γ RIIB) is required for obesity-induced systolic and diastolic hypertension. Tail-cuff systolic blood pressure (SBP) was measured in conscious, restrained Fc γ RIIB $^{+/+}$ and Fc γ RIIB $^{-/-}$ mice after control chow (CON) or high-fat diet (HFD) feeding for 16 weeks. The mice were acclimated to the BP monitor for 4 consecutive days before data were collected on the fifth day. Values are mean \pm SEM (n=12–13). **B to F**, A separate group of mice underwent carotid artery cannulation with a radiotelemetry device for measurement of SBP (**B**), diastolic blood pressure (DBP; **C**), mean arterial pressure (MAP; **D**), and heart rate (HR; **E**) after being on their respective diets for 12 weeks. In **B to F**, values are mean \pm SEM (n=4–7). In 2-way ANOVA analysis, cuff SBP and heart rate were significant for the effect of diet ($P < 0.05$). More importantly, DBP and MAP had a significant interaction of diet and genotype ($P < 0.05$). The effect of genotype was not significant in any comparison ($P > 0.05$). In post-test analysis, * $P < 0.05$ vs CON diet and † $P < 0.05$ vs Fc γ RIIB $^{+/+}$ HFD mice.

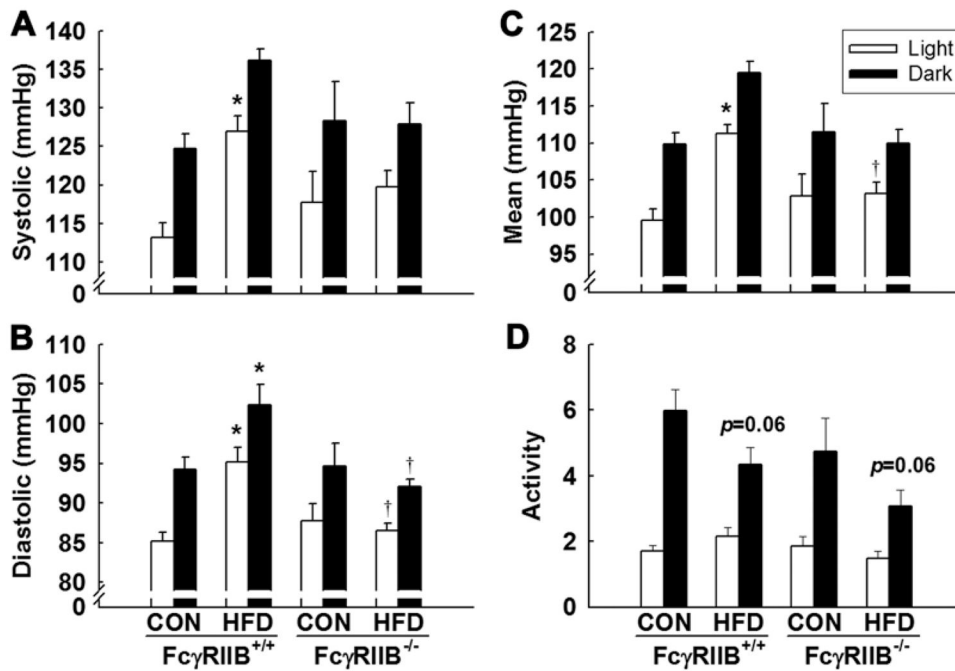


Figure 4. Modulation of blood pressure by high-fat diet (HFD) and Fc γ receptor IIB (Fc γ RIIB) occur during both light and dark cycles. **A** to **C**, Radiotelemetric systolic (**A**), diastolic (**B**), and mean arterial pressure (**C**) measurements in Fc γ RIIB^{+/+} and Fc γ RIIB^{-/-} mice after control chow (CON) or HFD feeding were grouped and averaged by 12-hour light (open bars) and 12-hour dark cycles (filled bars). **D**, Relative activity levels were also quantified. Values are mean \pm SEM (n=4-7), * P <0.05 vs CON diet and † P <0.05 vs Fc γ RIIB^{+/+} HFD mice.

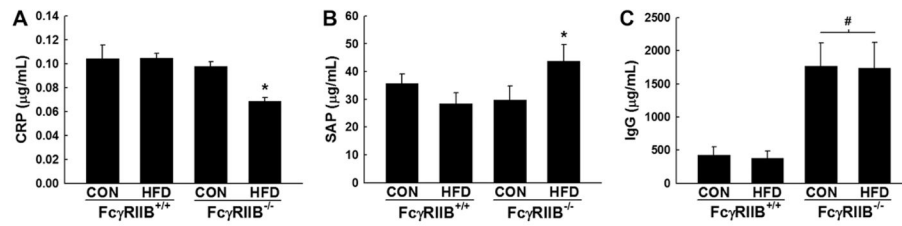


Figure 5.

Impact of high-fat diet (HFD)-induced obesity on serum C-reactive protein (CRP), serum amyloid P component (SAP), and total IgG. Concentrations of CRP (A), SAP (B), and total IgG (C) were measured by ELISA in serum obtained from Fc γ receptor IIB (Fc γ RIIB)^{+/+} and Fc γ RIIB^{-/-} mice after control chow (CON) or HFD feeding for 12 weeks. Values are mean \pm SEM (n=8–12), * P <0.05 vs CON diet, # P <0.05 vs Fc γ RIIB^{+/+}.

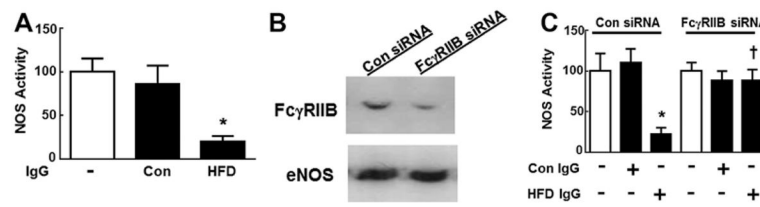


Figure 6.

IgG from high-fat diet (HFD)-fed mice antagonizes vascular endothelial growth factor (VEGF) activation of endothelial NO synthase (eNOS) via Fc γ receptor IIB (Fc γ RIIB). **A**, Bovine aortic endothelial cells (BAECs) were incubated with IgG isolated from control chow (CON) versus HFD-fed mice (10 μ g/mL), and VEGF (100 ng/mL) activation of eNOS was evaluated by quantifying 14 C-L-arginine conversion to 14 C-L-citrulline during 15-minute incubations (n=6–12). **B**, BAECs were transfected with either sham small interfering RNA (siRNA) or siRNA targeting Fc γ RIIB, and receptor abundance was evaluated by immunoblot analysis. **C**, The effects of CON vs HFD IgG on VEGF activation of eNOS were compared in cells transfected as in **B** (n=5). In **A** and **C**, values are mean \pm SEM, * P <0.05 vs CON IgG, † P <0.05 vs Con siRNA.