Molecular Medicine

CD36 Mediates the Cardiovascular Action of Growth Hormone–Releasing Peptides in the Heart


Abstract—Growth hormone–releasing peptides (GHRPs) are known as potent growth hormone secretagogues whose actions are mediated by the ghrelin receptor, a G protein–coupled receptor cloned from pituitary libraries. Hexarelin, a hexapeptide of the GHRP family, has reported cardiovascular activity. To identify the molecular target mediating this activity, rat cardiac membranes were labeled with a radioactive photoactivatable derivative of hexarelin and purified using lectin affinity chromatography and preparative gel electrophoresis. A binding protein of Mr, 84,000 was identified. The N-terminal sequence determination of the deglycosylated protein was identical to rat CD36, a multifunctional glycoprotein, which was expressed in cardiomyocytes and microvascular endothelial cells. Activation of CD36 in perfused hearts by hexarelin was shown to elicit an increase in coronary perfusion pressure in a dose-dependent manner. This effect was lacking in hearts from CD36-null mice and hearts from spontaneous hypertensive rats genetically deficient in CD36. The coronary vasoconstrictive response correlated with expression of CD36 as assessed by immunoblotting and covalent binding with hexarelin. These data suggest that CD36 may mediate the coronary vasospasm seen in hypercholesterolemia and atherosclerosis. (Circ Res. 2002;90:844-849.)

Key Words: acute coronary syndromes ■ growth hormone–releasing peptides ■ CD36 scavenger receptor

Growth hormone–releasing peptides (GHRPs) belong to a family of small synthetic peptides modeled from Met-enkephalin, which exhibit potent and dose-dependent GH-releasing activity and also significant prolactin (PRL)- and corticotropin (ACTH)-releasing effects.1 These neuroendocrine activities of GHRPs are mediated by the Ghrelin receptor, a specific G protein–coupled receptor2,3 that has been cloned from mammalian pituitary libraries and its subtypes identified in the pituitary gland, hypothalamus, and extra-hypothalamic brain regions by binding studies.4 Equilibrium displacement binding assays with GHRPs in different peripheral tissues have shown specific binding sites in the heart, adrenal, ovary, testis, lung, and skeletal muscle.5,6 Significantly, hexarelin, a hexapeptide member of the GHRPs family has been reported to feature cardiovascular activity. Long-term pretreatment of GH-deficient rats with this peptide provided protective effect on hearts from ischemia/reperfusion damages7 and prevented alterations of the vascular endothelium-dependent relaxant function.8 This protective effect was independent of any stimulation of the somatotropic axis,8,9 suggesting a direct action of hexarelin on specific cardiac receptors. Our initial characterization of a putative cardiac GHRP receptor revealed the existence of a binding site for a photoactivatable derivative of hexarelin with a Mr of 84,000 distinct from those identified in the pituitary.6,10 In the present study, we report the identification of the unique GHRP binding site in the heart as CD36, a multifunctional B-type scavenger receptor. We also demonstrate that the activation of this receptor by hexarelin induced a dose-dependent increase in coronary perfusion pressure in isolated perfused hearts. This effect was absent in hearts from CD36-deficient animals. These studies demonstrate a novel function for this scavenger receptor in the regulation of the vascular tone and suggest a potential role for CD36 in pathological vasospasm.

Materials and Methods

Animals
Hearts from male Sprague-Dawley rats (>400 g, n = 110; Charles River, St Constant, Quebec, Canada) were used as source of cardiac membranes for the purification of the hexarelin binding protein. Langendorff perfused heart experiments were performed on spontaneously hypertensive rats/NCrI BR (SHR/NCrI BR) (n = 5) and their control strain Wistar-Kyoto/NCrI BR (WKY/NCrI BR) (300 to 325 g, n = 5 Charles River) as well as on CD36-null mice (n = 8) and their control strain C57Bl/6j (n = 8).

Membrane Preparation
Animal use was in accordance with the Canadian council on animal care guidelines. All animals were anesthetized with sodium pento-
Receptor Binding and Photolabeling With $[^{125}]$-Tyr-Bpa-Ala-Hexarelin

The radiiodination procedure of the photocactivity ligand and the receptor binding assays were performed as described by Ong et al. Non-specific binding was defined as that not displaced by 10 μmol/L hexarelin.

Solubilization of Photolabeled Cardiac Membranes

Photolabeled cardiac membranes were solubilized in buffer A (50 mmol/L Tris-HCl pH 7.4, 100 mmol/L NaCl, 5 mmol/L MgCl$_2$, 2 mmol/L CaCl$_2$, 2 mmol/L MnCl$_2$, 1% Triton X-100, 1 mmol/L pepstatin, 1 μmol/L leupeptin, 0.1 μmol/L aprotinin, 0.4 μmol/L Pefabloc) for 20 hours at 4°C. The soluble fraction was obtained by centrifugation at 35,000g for 60 minutes at 4°C.

Purification of Labeled Protein and N-Terminal Sequencing

The solubilized cardiac membranes were consecutively incubated with wheat germ-agarose and lentil-Sepharose for 20 hours at 4°C. The lectin-coupled resins were washed with buffer A used in the solubilization step and the retained proteins were eluted with 0.3 M N-acetylglucosamine and 0.5 M α-methyl-d-mannopyranoside, respectively. After reduction with 5 mmol/L DTT and alkylation with 10 mmol/L iodoacetamide, the eluted proteins purified by lectin affinity chromatography were separated on 5% preparative SDS-PAGE. The radioactive band at 80 to 90 kDa was cut out of the gel and eluted in buffer B (100 mmol/L NH$_4$HCO$_3$, 0.1% SDS buffer). After acetonitrile precipitation, the sample was reconstituted in buffer C (100 mmol/L Na$_2$HPO$_4$ pH 7.0, 10 mmol/L EDTA, 10 mmol/L β-mercaptoethanol, 0.1% SDS, 0.6% octyglycoside), deglycosylated with 50 U of N-glycosidase F for 20 hours at room temperature, and repurified on 7.5% SDS-PAGE. The radio-active band at M, 57,000 corresponding to the deglycosylated binding protein of hexarelin was eluted in buffer B, and an aliquot sequenced by Edman degradation using an Hewlett-Packard G1000A protein sequencer in order to obtain the N-terminal sequence of the protein.

Western Blot

Cardiac membrane proteins were quantified by the bicinchoninic acid method, electrophoresed, and transferred to nitrocellulose membrane. CD36 was detected by a polyclonal rabbit anti-rat CD36 antibody and chemiluminescent enhancement. CD36/antibody complex was visualized with a peroxidase-linked crosslinked agarose coupled to the CD36 (164 to 182) peptide. The antibody generated in our laboratory by using the peptide CD36 (164 to 182) was used as initial purification step. Among the various lectins tested, wheat germ agglutinin and lens culinaris were found to yield the highest yield (30%). Solubilized photolabeled rat cardiac membranes were successively applied on wheat germ agglutinin and lens culinaris affinity columns. Figure 1, lane 2, depicts the enriched GHRP receptor fraction obtained in the eluate. This was further purified on semipreparative SDS-PAGE and the band of M, 84,000 (Figure 1, lane 3) was eluted from the gel and submitted to N-terminal digestion by using AvanTaq DNA polymerase (Clonetech). Oligonucleotide primers were designed against rat adipocytes CD36 nucleotide sequence$^{14}$ in which the forward primer 5'-GAATTCATATGCGCGGATTGGAGACCTAC-3' and the reverse primer 5'-CAGGCCGATATCAGTTTTTCCCGGTAC-3' contained Ndel and EcoRI endonuclease restriction sites, respectively. The resulting cDNA was subcloned into pET17b vector (Novagen). The construction was transformed into Escherichia coli JM109. Positive recombinant plasmid pCD36-pET17b selected by ampicillin resistance was transformed into E.coli BL21. The selected clones were subjected to induction of protein expression with IPTG 0.4 mmol/L for 2 hours at 37°C. E.coli cells were harvested, washed, and resuspended in Tris HCl pH 8.0 (50 mmol/L containing EDTA (5 mmol/L) and proteinase inhibitors (10 μmol/L) pepstatin 1.0, leupeptin 1.0, aprotinin 0.1, and Pefabloc 0.4. Cell lysis was performed by repeated cycles of freezing and thawing and sonication. The cell lysate was then centrifuged at 14,000g for 10 minutes, and the supernatant containing the recombinant soluble CD36 protein was submitted to photoaffinity labeling with the radiolabeled photocactivity hexarelin as described above. After the photolabeling step, the supernatant was first precleared by immunoprecipitation with addition of preimmune rabbit serum (30 μL) and protein A agarose (60 μL) (Roche Mannheim, Germany). The photolabeled protein was then immunoprecipitated using polyclonal rabbit anti-rat CD36 antibody (30 μL) and protein A agarose (60 μL). Both immunoprecipitates bound to protein A were washed and boiled with Tris HCl buffer pH 6.8 (62.5 mmol/L containing 2% SDS, 10% glycerol, 5% β-mercaptoethanol, and 0.00125% bromophenol blue. The eluted radiolabeled material were resolved on SDS-PAGE for autoradiography. E.coli containing only the pET17b vector were processed as described above as negative control.

Experimental Protocol With Langendorff Perfused Hearts

Animal use was in accordance with the Canadian council on animal care guidelines. Rats (300 to 350 g) and mice (25 to 30 g) were narcotized with CO$_2$ until complete loss of consciousness and promptly decapitated. Hearts were rapidly immersed into ice-cold Krebs-Henseleit buffer, mounted within 2 minutes on the Langendorff apparatus, and perfused at a constant flow rate by means of a digital peristaltic pump as previously described.$^{14}$ The normal perfusion solution consisted of a modified Krebs-Henseleit buffer containing (in mmol/L): NaCl 118.0, KCl 4.0, CaCl$_2$ 2.5, KH$_2$PO$_4$ 1.2, MgSO$_4$ 1.0, NaHCO$_3$ 24.0, d-glucose 5.0, and pyruvate 2.0, gassed with 95% O$_2$/5% CO$_2$ (pH 7.4), and kept at a constant temperature of 37°C. The perfusion flow rate was between 12 to 15 mL/min$^{-1}$ in rat hearts (yielding a coronary perfusion pressure of 75 mm Hg) and was set at 3 mL/min$^{-1}$ for mouse hearts. Isovolumetric left ventricular pressure, its first derivative (dP/dt), and heart rate were all measured from a fluid-filled latex balloon inserted into the left ventricle and connected to a pressure transducer. The volume of the balloon was adjusted to obtain a diastolic pressure around 10 mm Hg. Coronary perfusion pressure was recorded with a second pressure transducer connected to a side-port of the perfusion line. All these cardiac functional variables were recorded on a polygraph system (Grass Model 79 polygraph, AstroMed Inc). After a 20-minute stabilization period, dose-response curves to hexarelin were charted by successive infusions of increasing concentrations of the peptide administered through a Y connector of the aortic cannula with a syringe pump. Each infusion was maintained for 5 to 10 minutes, enough to reach steady state.

Results

Affinity Purification of GHRP Receptor in Cardiac Membranes

In our previous study,$^4$ the cardiac binding sites for hexarelin were identified as a heavily glycosylated membrane-associated protein. Lectin affinity chromatography was thus used as initial purification step. Among the various lectins tested, wheat germ agglutinin and lens culinaris were found to give the highest yield (30%). Solubilized photolabeled rat cardiac membranes were successively applied on wheat germ agglutinin and lens culinaris affinity columns. Figure 1, lane 2, depicts the enriched GHRP receptor fraction obtained in the eluate. This was further purified on semipreparative SDS-PAGE and the band of M, 57,000 (Figure 1, lane 4) was eluted from the gel and submitted to N-terminal digestion by using AvanTaq DNA polymerase (Clonetech). Oligonucleotide primers were designed against rat adipocytes CD36 nucleotide sequence$^{14}$ in which the forward primer 5'-GAATTCATATGCGCGGATTGGAGACCTAC-3' and the reverse primer 5'-CAGGCCGATATCAGTTTTTCCCGGTAC-3' contained Ndel and EcoRI endonuclease restriction sites, respectively. The resulting cDNA was subcloned into pET17b vector (Novagen). The construction was transformed into Escherichia coli JM109. Positive recombinant plasmid pCD36-pET17b selected by ampicillin resistance was transformed into E.coli BL21. The selected clones were subjected to induction of protein expression with IPTG 0.4 mmol/L for 2 hours at 37°C. E.coli cells were harvested, washed, and resuspended in Tris HCl pH 8.0 (50 mmol/L containing EDTA (5 mmol/L) and proteinase inhibitors (10 μmol/L) pepstatin 1.0, leupeptin 1.0, aprotinin 0.1, and Pefabloc 0.4. Cell lysis was performed by repeated cycles of freezing and thawing and sonication. The cell lysate was then centrifuged at 14,000g for 10 minutes, and the supernatant containing the recombinant soluble CD36 protein was submitted to photoaffinity labeling with the radiolabeled photocactivity hexarelin as described above. After the photolabeling step, the supernatant was first precleared by immunoprecipitation with addition of preimmune rabbit serum (30 μL) and protein A agarose (60 μL) (Roche Mannheim, Germany). The photolabeled protein was then immunoprecipitated using polyclonal rabbit anti-rat CD36 antibody (30 μL) and protein A agarose (60 μL). Both immunoprecipitates bound to protein A were washed and boiled with Tris HCl buffer pH 6.8 (62.5 mmol/L containing 2% SDS, 10% glycerol, 5% β-mercaptoethanol, and 0.00125% bromophenol blue. The eluted radiolabeled material were resolved on SDS-PAGE for autoradiography. E.coli containing only the pET17b vector were processed as described above as negative control.
sequence analysis by Edman degradation. The amino acid sequence obtained was GCDRNXGLITGAVIGAVLAFGLMPVV, which was found identical to the N-terminal sequence of rat CD36 antigen. 15,16

CD36 Photolabeling and Immunoblotting in SHR and CD36-Null Mice

To further demonstrate that CD36 is the binding site for GHRP in the heart, we performed photolabeling studies of cardiac membrane preparations isolated from 2 different models of CD36 deficiency: CD36-null mice by homologous recombination and rats from the SHR/NCrlBR strain. These rats have been shown to have a defective CD36 gene resulting in the generation of multiple splice variants of CD36 cDNA, with the corresponding proteins being undetectable in the plasma membrane of their adipocytes.17 Covalent photolabeling of cardiac membranes derived from CD36-deficient rats and CD36-null mice with [125 I]-Tyr-Bpa-Ala-Hexarelin did not feature any specific binding signal, compared with those from control strains WKY/NCrlBR and C57Bl6, which showed a specific photolabeled band of Mr 84 000 (Figure 2).

Western blot analysis of cardiac membrane proteins from SHR/NCrlBR and CD36 knockout mice using a polyclonal rabbit anti-rat CD36 antibody showed no expression of CD36, which contrasted with the high level of CD36 protein immunodetected at M, 84 000 in cardiac membranes from WKY/NCrlBR and C57Bl6 control strains (Figure 3). Taken together, the data of photolabeling and Western blot analysis support the evidence of a unique binding protein for hexarelin corresponding to CD36 in the heart.

Identification of CD36 as Binding Site of Hexarelin

To confirm the identity of CD36 as the interacting protein of [125 I]-Tyr-Bpa-Ala-Hexarelin derivative, we have expressed the extracellular binding domain of this scavenger receptor using E coli BL21 as vector. The photoaffinity labeling of the nonglycosylated soluble form of CD36 was carried out as described above. The immunoprecipitated material using the polyclonal rabbit anti-rat CD36 antibody, resolved by SDS-PAGE, featured a unique radioactive band at Mr 51 000 as shown in the autoradiogram (Figure 4). This band was not observed from the immunoprecipitated material using the nonimmune rabbit serum. The immunoprecipitation of the photoaffinity cross-linking of [125 I]-Tyr-Bpa-Ala-Hexarelin to the soluble form of CD36 generated a radiolabeled band

![Figure 1](https://circres.ahajournals.org/)

**Figure 1.** SDS-PAGE analysis of the successive steps of purification of the binding site of GHRP from rat heart. A, Coomassie blue staining of the gel; B, autoradiogram of the gel. Lane 1, Soluble fraction in Triton X-100 of the photolabeled cardiac membranes. Lane 2, Eluate from the lectin affinity chromatography. Lane 3, Purified fraction after the semipreparative SDS-PAGE step. Lane 4, Soluble fraction containing the deglycosylated photolabeled GHRP receptor.

![Figure 2](https://circres.ahajournals.org/)

**Figure 2.** Covalent photolabeling of cardiac membranes with [125 I]-Tyr-Bpa-Ala-Hexarelin in the absence (--) or presence (+) of an excess of hexarelin (10 μmol/L). A, Membranes from the SHR/NCrlBR and WKY/NCrlBR strains. B, Membranes from CD36-null mice (--/--) and their wild-type littermates (+/+).

![Figure 3](https://circres.ahajournals.org/)

**Figure 3.** Immunodetection of CD36 in cardiac membranes. A, Membranes from the SHR/NCrlBR and WKY/NCrlBR strains. B, Membranes from CD36-null mice (--/-) and their wild-type littermates (+/+).

![Figure 4](https://circres.ahajournals.org/)

**Figure 4.** Immunoprecipitation of soluble CD36 recombinant protein photolabeled with [125 I] Tyr-Bpa-Ala-Hexarelin. Lane 1, Immunoprecipitation with polyclonal rabbit anti-rat CD36 antibody. Lane 2, Immunoprecipitation with polyclonal rabbit anti-rat CD36 antibody from the preprecipitation step. Lane 3, Immunoprecipitation with polyclonal rabbit anti-rat CD36 antibody from the lysate of E coli transfected with pET17b vector only (negative control).
GHRP-Induced Coronary Vasoconstriction Is Mediated by CD36

We have previously reported the vasoconstrictive effect of hexarelin in the perfused rat heart model. To assess whether this coronary vasoconstriction was mediated by CD36, dose-response curves to hexarelin were performed in the perfused Langendorff hearts collected from SHR/NcrlBR, C57Bl/6 control mice, and CD36-null rats. Hexarelin induced a dose-dependent increase in coronary perfusion pressure in hearts from C57Bl/6 mice that was statistically significant only in the first series of experiments. Heart rate, minute^-1

<table>
<thead>
<tr>
<th>Hexarelin</th>
<th>Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>1840±160</td>
</tr>
<tr>
<td>Maximal</td>
<td>1840±160</td>
</tr>
</tbody>
</table>

Values are mean±SEM. SHR indicates spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; and P, probability of SHR being different from WKY, obtained with a 2-sample unpaired t-test with separate variance (n=5 to 7 hearts per strain).

Figure 5. Change in coronary perfusion pressure (CPP) induced by increasing concentrations of hexarelin (left) and angiotensin II (Ang II, right) in hearts from SHR/NcrlBR (open circles, n=5) and WKY/NcrlBR (filled circles, n=5). Concentrations for which a significant (P<0.05) difference was found between groups (analysis of variance).

WKY/NcrlBR was markedly blunted in hearts from CD36-deficient rats. Hexarelin had no chronotropic or inotropic effects in rat hearts (Table 1). The potent vasoconstrictor angiotensin II induced comparable response in hearts isolated from both strains (Figure 5, right panel), suggesting that the blunted coronary response to hexarelin from SHR/NcrlBR was not due to nonspecific effects of the elevated blood pressure in these animals.

CD36-null mice were used as a second model of CD36 deficiency. These animals had normal hearts, as shown by the comparable functional variable values between CD36-null and C57Bl/6 control mice (Table 2). A lower resting coronary resistance was observed in CD36-null mice, which was statistically significant only in the first series of experiments. Hexarelin induced a dose-dependent increase in coronary perfusion pressure in hearts from C57Bl/6 mice that was totally absent in hearts lacking the CD36 protein (Figure 6, left panel). In comparison, angiotensin II induced a dose-dependent vasoconstriction statistically comparable in hearts from both strains of mice (Figure 6, right panel). Hexarelin also induced negative chronotropic (statistically significant in C57Bl/6 mice only) and inotropic effects in mouse hearts (Table 2).

**Discussion**

Growth hormone (GH) secretion is well known to be regulated by GH-releasing hormone (GHRH) and somatostatin at the hypothalamic level. The discovery of growth hormone–releasing peptides has revealed the existence of a third pathway for the modulation of GH release. This action on GH release is mediated by a G protein–coupled receptor of M, 41,000, which is mainly expressed at the hypothalamic and pituitary levels. Besides this neuroendocrine effect of GHRPs, it was reported that a long-term treatment with hexarelin, a hexapeptide member of the GHRP family, featured a protective effect against postischemic dysfunction in rats. Because no apparent stimulation of the growth

**TABLE 1. Basal Functional Variable Values and Values Under Maximal Stimulation With Either Hexarelin or Angiotensin II in Hearts From SHR and WKY**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart mass, g</td>
<td>1.86±0.04</td>
<td>1.91±0.02</td>
</tr>
<tr>
<td>Heart rate, minute^-1 Basal</td>
<td>237±9</td>
<td>221±10</td>
</tr>
<tr>
<td>Heart rate, minute^-1 Maximal</td>
<td>235±5</td>
<td>223±13</td>
</tr>
<tr>
<td>Maximum dP/dt, mm Hg second^-1 Basal</td>
<td>2320±174</td>
<td>2070±124</td>
</tr>
<tr>
<td>Maximum dP/dt, mm Hg second^-1 Maximal</td>
<td>1840±160</td>
<td>1981±168</td>
</tr>
<tr>
<td>Coronary resistance, mm Hg min mL^-1 Basal</td>
<td>5.07±0.20</td>
<td>6.06±0.15</td>
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<tr>
<td>Coronary resistance, mm Hg min mL^-1 Maximal</td>
<td>9.68±0.60*</td>
<td>7.22±0.32*</td>
</tr>
</tbody>
</table>

**Values are mean±SEM. SHR indicates spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; and P, probability of SHR being different from WKY, obtained with a 2-sample unpaired t-test with separate variance (n=5 to 7 hearts per strain).**

*P<0.05 compared with the corresponding basal value (paired t-test); †P=0.01 when hearts treated with hexarelin and angiotensin II are pooled.
TABLE 2. Basal Functional Variable Values and Values Under Maximal Stimulation With Either Hexarelin or Angiotensin II in Hearts From CD36 Knockout and Control Mice

<table>
<thead>
<tr>
<th></th>
<th>C57BL/6</th>
<th>CD36/−/−</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Hexarelin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart mass, mg</td>
<td>161±7</td>
<td>158±6</td>
<td>0.75</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
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<tr>
<td>Basal</td>
<td>343±10</td>
<td>332±19</td>
<td>0.61</td>
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<tr>
<td>Maximal</td>
<td>319±13</td>
<td>301±35</td>
<td>0.64</td>
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<tr>
<td>Maximum dP/dt, mm Hg s⁻¹</td>
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</tr>
<tr>
<td>Basal</td>
<td>1648±291</td>
<td>1358±69</td>
<td>0.36</td>
</tr>
<tr>
<td>Maximal</td>
<td>1151±174</td>
<td>945±85†</td>
<td>0.31</td>
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<tr>
<td>Coronary resistance, mm Hg min mL⁻¹</td>
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<td></td>
</tr>
<tr>
<td>Basal</td>
<td>26.7±1.9</td>
<td>21.3±1.1</td>
<td>0.03†</td>
</tr>
<tr>
<td>Maximal</td>
<td>32.3±3.3*</td>
<td>20.5±2.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
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</tr>
<tr>
<td>Heart mass, mg</td>
<td>154±11</td>
<td>173±7</td>
<td>0.15</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
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<tr>
<td>Basal</td>
<td>308±17</td>
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<tr>
<td>Maximal</td>
<td>339±20</td>
<td>358±23</td>
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<tr>
<td>Maximum dP/dt, mm Hg s⁻¹</td>
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<tr>
<td>Basal</td>
<td>2281±407</td>
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<tr>
<td>Maximal</td>
<td>1874±303</td>
<td>1967±413</td>
<td>0.86</td>
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<td>Coronary resistance, mm Hg min mL⁻¹</td>
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<tr>
<td>Basal</td>
<td>28.2±3.4</td>
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<tr>
<td>Maximal</td>
<td>35.2±5.4*</td>
<td>29.4±5.0*</td>
<td>0.44</td>
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Values are mean±SEM. P indicates probability of C57BL/6 being different from CD36/−/−, obtained with a 2-sample unpaired t test with separate variance (n=8 to 9 hearts per strain).

*P<0.05 compared with the corresponding basal value (paired t test); †P=0.09 when hearts treated with hexarelin and angiotensin II are pooled.

Figure 6. Change in coronary perfusion pressure (CPP) induced by increasing concentrations of hexarelin (left) and angiotensin II (Ang II, right) in hearts from CD36/−/− (open circles, n=5) and C57BL/6 (filled circles, n=7) mice. *Concentrations for which a significant (P<0.05) difference was found between groups (analysis of variance).

Acknowledgments

This work was supported by grants from the Canadian Institutes of Health Research (CIHR)–University Program (UOP-50059) (H.O.), Pharmacia-Upjohn, Stockholm, Sweden, the CIHR (MOP-15047)
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_Circ Res_. 2002;90:844-849; originally published online March 21, 2002;
doi: 10.1161/01.RES.000016164.02525.B4

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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