Simvastatin Inhibits Central Sympathetic Outflow in Heart Failure by a Nitric-Oxide Synthase Mechanism

Lie Gao, Wei Wang, and Irving H. Zucker

Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, Nebraska

Received December 28, 2007; accepted April 23, 2008

ABSTRACT

Our previous study demonstrated that oral treatment with simvastatin (SIM) suppressed renal sympathetic nerve activity (RSNA) in the rabbits with chronic heart failure (CHF). The purpose of this experiment was to determine the effects of direct application of SIM to the central nervous system on RSNA and its relevant mechanisms. Experiments were carried out on 21 male New Zealand White rabbits with pacing-induced CHF. The CHF rabbits received infusion of vehicle, SIM, or SIM + N\(^-\)nitro-L-arginine methyl ester into the lateral cerebral ventricle via osmotic minipump for 7 days. We found that 1) in CHF rabbits, intracerebroventricular infusion of SIM significantly suppressed basal RSNA (1st day 69.5 ± 8.9% maximum; 7th day 26.0 ± 6.0% maximum; \(P < 0.05\), \(n = 7\)) and enhanced arterial baroreflex function starting from the 2nd day and lasting through the following 5 days; 2) statin treatment significantly up-regulated neuronal nitric-oxide synthase (nNOS) protein expression in the rostral ventrolateral medulla (RVLM) (control, \(n = 6\), 0.12 ± 0.04; SIM-treated, \(n = 7\), 0.31 ± 0.05, \(P < 0.05\)); 3) in CATH.a neurons, incubation with SIM significantly up-regulated the nNOS mRNA expression, which was blocked by coinubcation with mevalonate, farnesyl-pyrophosphate, or geranylgeranyl-pyrophosphate; and 4) incubation with Y-27632 [(\(R\))-trans-N-(4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide] significantly up-regulated nNOS mRNA expression in these neurons. These results suggest that central treatment with SIM decreased sympathetic outflow in CHF rabbits via up-regulation of nNOS expression in RVLM, which may be due to the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase and a decrease in Rho kinase by SIM.

Chronic heart failure (CHF) is characterized by both sympathetic-excitation (Packer, 1992) and blunted arterial baroreflex function (DiBona and Sawin, 1995). Our previous studies demonstrated that oral treatment with the HMG-CoA reductase inhibitor, simvastatin (SIM), improved baroreflex function in the rabbits with CHF (Pliquett et al., 2003). In previous experiments, we have demonstrated that these therapeutic effects of SIM correlated with changes in several important signaling molecules in the rostral ventrolateral medulla (RVLM) of rabbits with CHF (Gao et al., 2005a). These experiments were based on systemic (oral) administration of SIM. Therefore, it is difficult to determine whether these effects were mediated by central or peripheral mechanisms following oral administration of SIM. Because SIM has been demonstrated to permeate the blood-brain barrier (Saheki et al., 1994), we postulated that the above effects of oral SIM were mediated, at least partially, by central mechanisms. Our first hypothesis in the current experiment was that direct administration of SIM into the brain would reduce sympathetic nerve activity in the CHF state.

There is considerable evidence suggesting that nitric oxide (NO) in the central nervous system, especially in the brain stem, plays an important role in the regulation of sympathetic outflow and blood pressure (Zanninger, 1999; Krukoff, 1999). The RVLM is the last relay station in the brain to integrate sympathetic outflow (Dampney, 1994). The sympathetic premotor neurons of the RVLM provide the major tonic excitatory input to sympathetic preganglionic neurons in the spinal cord (Guertzenstein and Silver, 1974). Chan et al. (2001, 2003) have demonstrated the existence of nitric-oxide synthase (NOS) in the RVLM. On the other hand, Bredt et al. (1990) demonstrated that NO synthase in the brain is exclusively associated with discrete neuronal populations. Treatment with a precursor of NO (Shapoval et al., 1991) or an NO donor of NO increased neuronal activity in the RVLM, which is a target organ for NO. The effect of NO on the RVLM was blocked by L-NAME, the L-NMMA, or the inhibitor of the NOS enzyme, which suggests that NO synthesized in situ is responsible for the effect of NO on the RVLM. Therefore, we conclude that the effects of SIM on the RVLM could be due to the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase and a decrease in Rho kinase by SIM.

**ABBREVIATIONS:** CHF, chronic heart failure; SIM, simvastatin; FPP, farnesyl-pyrophosphate; RVLM, rostral ventrolateral medulla; RT-PCR, reverse transcription-polymerase chain reaction; GGPP, geranylgeranyl pyrophosphate; NOS, nitric-oxide synthase; eNOS, endothelial NOS; nNOS, neuronal NOS; Y-27632, (\(R\))-trans-N-(4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide; MAP, mean arterial pressure; HR, heart rate; CSF, cerebrospinal fluid; RSNA, renal sympathetic nerve activity; L-NAME, N\(^-\)nitro-L-arginine methyl ester; ROCK, Rho-associated kinase; AP, arterial pressure.
of each experiment, the placement of the cannula was confirmed by injection of 50 μl of 2% Pontamine Sky Blue into the lateral cerebral ventricle via the cannula.

Arterial Pressure, Heart Rate, and Renal Sympathetic Nerve Recording. A catheter connected to a radiotelemetry unit (Data Sciences International, St. Paul, MN) was inserted into the descending aorta via a branch of the right femoral artery for direct measurement of arterial pressure (AP). HR was derived from the AP pulse using a PowerLab (model 8S; AD Instruments Inc., Colorado Springs, CO) data acquisition system. Renal sympathetic nerve recording was carried out in the conscious state as described previously (Liu and Zucker, 1999).

Evaluation of Arterial Baroreflex Function. AP, HR, and RSNA were recorded on a Powerlab system. An intravenous infusion of sodium nitroprusside and then phenylephrine was used to induce alterations of AP. Baroreflex sensitivity was expressed as the slope of the linear regression relating changes in integrative RSNA to changes in MAP from the lowest AP induced by nitroprusside to the peak pressure induced by phenylephrine.

Preparation of RVLVM Tissue. At the end of experiment, the rabbits were euthanized with pentobarbital sodium. The brain was removed and immediately frozen on dry ice, blocked in the coronal plane, and sectioned at 150-μm thickness in a cryostat. The bilateral RVLVM areas (2.0–3.5 mm from the obex, 2.5–4.0 mm from middle line, and within the ventrolateral area of section) were punched out using a 15-gauge needle stub (inner diameter of 1.5 mm) for the analysis of protein of nNOS.

Western Blot Analysis for nNOS. Protein from RVLVM of rabbits was extracted using radioimmunoprecipitation assay buffer, the concentration of which was then measured using a protein assay kit (Pierce, Rockford, IL) and adjusted to the same with equal volumes of 2 × 4% SDS sample buffer. The samples were then boiled for 5 min following by loading on the 7.5% SDS-polyacrylamide gel electrophoresis gel (5 μg of protein/30 μl/well) for electrophoresis using Bio-Rad mini gel apparatus (Bio-Rad, Hercules, CA) at 40 mA/each gel for 45 min. The fractionized proteins on the gel then were electrotherocally transferred onto the polyvinylidine difluoride membrane (Millipore Corporation, Billerica, MA) at 300 mA for 90 min. The membrane was probed with primary antibody (nNOS mouse IgG2a, 1:1000; BD Biosciences, San Jose, CA) and secondary antibody (goat anti-mouse IgG-HRP, 1:2500; Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and then treated with enhanced chemiluminescence substrate (Pierce) for 5 min at room temperature. The bands in the membrane were visualized and analyzed using UVP Biolimaging Systems (Upland, CA).

CATH.a Cell Culture. A neuronal cell line (CATH.a) was purchased from American Type Culture Collection (Manassas, VA) and grown in RPMI 1640 containing 8% horse serum, 4% fetal bovine serum, and 1% penicillin-streptomycin at 37°C in a humidified atmosphere equilibrated with 5% CO2. After subculture, cells were plated on polystyrene tissue culture dishes at a density of 1 × 10^5 cells/100-mm plate with N-6,2'-dibutylryladenosine 3',5'-cyclic monophosphate (1 mM; Sigma-Aldrich, St. Louis, MO) to grow for 2 days to obtain differentiated CATH.a cells and then were treated with SIM alone or plus mevalonate, farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), or Y-27632 for 1 to 3 days.

Real-time RT-PCR Analysis of nNOS mRNA. Total RNA from CATH.a cell pellets for real-time RT-PCR was extracted using RNeasy columns (Qiagen, Valencia, CA), which then was reverse-transcribed into double-stranded cDNA. Real-time RT-PCR was carried out using the thermocycler (PTC-200 Peltier Thermal Cycler with CHROMO 4 Continuous Fluorescence Detector; Bio-Rad) according to the manufacturer’s recommendations. Cycle numbers obtained at the log-linear phase of the reaction were plotted against a standard curve prepared with serially diluted control samples. Expression of target genes was normalized by GAPDH levels. The primers and probes used in this experiment were designed using software on the website (https://www.genscript.com/sso-bin/app/primer) and synthesized by the Epplley Institute Molecular Biology...
Core Laboratory, University of Nebraska Medical Center. Table 1 shows the gene-specific primers and probes. The primers and probes to detect gene expression in the CATH.a neuron sample were de-
signed according to the mouse gene sequences because these neurons are derived from a transgenic mouse brain locus coeruleus.

**Statistical Analysis.** Data are expressed as the mean ± S.E. The differences between groups were determined with a one-way analy-
sis of variance followed by the Student's Newman-Keuls test for analysis of significance. The differences before and after intracerebroventricular infusion in each group were analyzed with a paired t test. Statistical significance was defined as *P* < 0.05.

**Results**

**Body Weight, Ratio of Organ Weight to Body Weight, Hemodynamics, and Echo Data.** Table 2 shows the values for body weight, ratio of organ weight to body weight, hemodynamics, and echo data in the CHF rabbits from the three groups studied. Hemodynamics and echo data were measured, respectively, before and at day 7 post- intracerebroventricular infusions of reagents. Whereas only CHF rabbits were studied, they exhibited higher ratios of heart and lung weight to body weight, higher left ventricular end-diastolic pressure and left ventricular end-diastolic diameter, and lower ejection fraction compared with normal rabbits from previous studies in our laboratory (Gao et al., 2005a). There were no significant changes in these parameters between the three groups of rabbits studied here.

**Intracerebroventricular Infusion of SIM Decreases Baseline RSNA.** An original recording of AP, HR, and RSNA responses before (Fig. 3, A and C) or after (Fig. 3, B and D) intracerebroventricular infusion of vehicle (Fig. 3, A and B) or SIM (Fig. 3, C and D) in conscious CHF rabbits is shown in Fig. 1. Compared with Fig. 1A (before infusion), intracerebroventricular infusion of vehicle (artificial CSF) did not exhibit any effects on the RSNA (Fig. 1D). In contrast, from Fig. 1D, we can clearly see a noticeable increase in RSNA beginning at day 2, which was sustained up to day 7, compared with either day 0 or vehicle treatment. On the other hand, intracerebroventricular infusion of SIM plus l-NAME prevented the sympatho-inhibition of SIM alone. This suggests that the response to SIM was, at least in part, due to an NO mechanism.

**Intracerebroventricular Infusion of SIM Increases RSNA.** Figure 2 is the grouped data illustrating the effects of intracerebroventricular infusion of SIM on basal RSNA in conscious CHF rabbits. From this figure, we can see that intracerebroventricular infusion of SIM caused a decrease in RSNA beginning at day 2, which was sustained up to day 7, compared with either day 0 or vehicle treatment. On the other hand, intracerebroventricular infusion of SIM plus l-NAME prevented the sympatho-inhibition of SIM alone. This suggests that the response to SIM was, at least in part, due to an NO mechanism.

**Hemodynamics and Echo Data.** Hemodynamics and Echo data were measured, respectively, before and at day 7 post- intracerebroventricular infusion in each group were analyzed with a paired *t* test. Statistical significance was defined as *P* < 0.05.

**Table 1**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward Primers (5’–3’)</th>
<th>Reverse Primers (3’–5’)</th>
<th>Probes</th>
<th>Amplicon Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse nNOS (AK141904)</td>
<td>ATCACAGGCACAAATGGGAGA</td>
<td>TGATCCACTGCCTGTATTAAA</td>
<td>TGGGT CCTCCACAGGGACCC</td>
<td>123</td>
</tr>
<tr>
<td>Mouse GAPDH (NM_001001303)</td>
<td>ACAAATTGCGCATTGTGGGA</td>
<td>GATGCAGGGATGTGTTCGT</td>
<td>CATGCCATCAGTGGACCACCA</td>
<td>133</td>
</tr>
</tbody>
</table>

**nt**, nucleotide numbers.

**Table 2**

<table>
<thead>
<tr>
<th>Vehicle Treatment (n = 6)</th>
<th>Simvastatin Treatment (n = 7)</th>
<th>Simvastatin + l-NAME Treatment (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
<td><strong>Before</strong></td>
</tr>
<tr>
<td>BW (kg)</td>
<td>3.9 ± 0.4</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>HW/BW (g/kg)</td>
<td>3.4 ± 0.3</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>LW/BW (g/kg)</td>
<td>5.4 ± 0.3</td>
<td>5.1 ± 0.4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>70.6 ± 3.4</td>
<td>73.2 ± 5.9</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>227.9 ± 7.5</td>
<td>241.3 ± 10.2</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>15.4 ± 2.2</td>
<td>14.4 ± 2.5</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>18.8 ± 0.9</td>
<td>17.6 ± 0.7</td>
</tr>
<tr>
<td>EF (%)</td>
<td>36.3 ± 4.1</td>
<td>34.8 ± 5.3</td>
</tr>
</tbody>
</table>

BW, body weight; HW, heart weight; LW, lung weight; LVEDP, left ventricular end-diastolic pressure; LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction.
nNOS protein from the RVLM of rabbits receiving the intracerebroventricular infusion of SIM compared with that from the vehicle-treated rabbits. Given that SIM decreased basal RSNA and improved the baroreflex function rabbits from day 2 after treatment, we measured the nNOS protein expression in the RVLM of three CHF rabbits after 48 h of intracerebroventricular infusion of SIM. We found that the nNOS protein expression was up-regulated after 48 h of SIM treatment (the ratio of nNOS to GAPDH: 0.27 ± 0.06 in 48-h SIM treatment, n = 3; 0.31 ± 0.05 in 7-day SIM treatment, n = 7; 0.12 ± 0.04 in vehicle treatment, n = 6).

It is worthy to note that we also measured nNOS protein expression in the hypothalamus, another sympathetic-related nucleus, in these rabbits. We found higher expression of
Fig. 2. Group data showing the time course of intracerebroventricular infusion of SIM-induced decrease in renal sympathetic nerve activity and blockade by L-NAME. *, P < 0.05 compared with vehicle group; #, P < 0.05 compared with pre-SIM treatment in the same group; @, P < 0.05 compared with SIM group. n = 6 in vehicle group; n = 7 in SIM group; n = 5 in SIM + L-NAME group.

Discussion

Our previous studies have demonstrated that oral treatment with SIM normalized sympathetic outflow and restored arterial baroreflex function in rabbits with pacing-induced CHF via an inhibition of angiotensin II mechanisms and reactive oxygen species in the RVLM (Pliquett et al., 2003; Gao et al., 2005a). In the current study, we further found that direct intracerebroventricular infusion of SIM also exhibited a beneficial effect on sympathetic nerve activity and baroreflex function in the CHF state. This was accompanied by an up-regulation of nNOS protein expression in the RVLM. Moreover, intracerebroventricular coinfusion of SIM and L-NAME completely abolished the effect of SIM on sympathetic nerve activity and baroreflex function but had no effects on nNOS expression. These results strongly suggest that increased central NO production is another critical pathway to normalize sympathetic nerve activity in the CHF state and that the elevated NO production at least partially resulted from the up-regulation of nNOS expression in the RVLM.

As indicated above, NOS and NO in the RVLM have a major influence on sympathetic nerve activity in both physiological and pathological states. Vincent and Kimura (1992) first demonstrated the presence of NOS-immunoreactive neurons in the RVLM of rats, which was further confirmed by Ohta et al. (1993) and Simonian and Herbison (1996). This morphological evidence implies a potentially functional involvement of RVLM local NO in the regulation of sympathetic outflow. Indeed, microinjection of sodium nitroprusside, a donor of NO, or L-arginine, a precursor for NO, into the RVLM of normal cats induced a reduction in RSNA and MAP (Shapoval et al., 1991). In anesthetized rats, microinjections of NO donors and NOS inhibitors into the RVLM exhibited sympatho-inhibitory and sympatho-excitatory effects, respectively (Zanninger et al., 1995). In the current experiment, we found that intracerebroventricular infusion of SIM up-regulated nNOS protein expression in the RVLM of CHF rabbits and the simultaneously decreased RSNA, suggesting that SIM-induced suppression of sympathetic outflow was mediated, at least partially, by the NO/nNOS pathway. Indeed, the NOS inhibitor, L-NAME, abolished the effects of SIM on sympathetic nerve activity when coinfused with SIM, providing further evidence demonstrating the potential involvement of NO in this SIM effect. Moreover, functional data from this experiment show that the SIM-induced decrease in sympathetic nerve activity presented as early as day 2 after treatment and was sustained up to day 7 after SIM treatment. This was paralleled by an up-regulated nNOS protein expression at days 2 and 7 after SIM treatment. Recently, Kishi et al. (2001) reported that gene transfer-induced overexpression of eNOS in the bilateral RVLM significantly decreased AP, HR, and sympathetic nerve activity in conscious rats, providing a more direct involvement of the RVLM NOS expression in the regulation of sympathetic outflow. They further demonstrated that eNOS overexpression-induced inhibition of sympathetic activity was mediated by an increased release of GABA in the RVLM. However, using antibodies from BD Biosciences, we did not detect the NOS and eNOS protein expressions in the RVLM of rabbits in this current experiment (data not shown).

Another novel finding in this experiment is that intracerebroventricular infusion of SIM improved arterial baroreflex function of CHF rabbits. This may also be mediated by the NO/nNOS pathway in the RVLM because it was reversed by L-NAME treatment. Indeed, overexpression of eNOS or nNOS by gene transfer into the RVLM has been demon-
strated to improve the impaired arterial baroreflex function in either spontaneously hypertensive rats (Kishi et al., 2003) or CHF rats (Wang et al., 2003). Therefore, we postulated that SIM would suppress sympathetic nerve activity and the improved arterial baroreflex function. Based on the known effects of statins, we hypothesized that both of these effects would be due to up-regulation of nNOS expression in the RVLM. It is well documented that sympathetic nerve activity and arterial baroreflex function are tightly interdependent. That is, activation of the arterial baroreflex markedly inhibits sympathetic outflow, and sympathetic overactivity impairs baroreflex function. However based on the current ex-

Fig. 3. Original recording of arterial blood pressure changes induced by intravenous infusion of phenylephrine and attendant reflex RSNA and HR responses before (A and C) and after (B and D) vehicle (A and B) and SIM (C and D) treatment in the CHF rabbits. Note the improved reflex sympato-inhibition and bradycardia responses to the phenylephrine-induced pressor effect after SIM treatment (D) compared with either pre-SIM treatment (D) or vehicle treatment (B).
Experiments, it is difficult to determine whether these are two independent processes after treatment with SIM in CHF rabbits. Comparing the data in Figs. 2 and 4, we noted that the slope of the baroreflex was gradually increased from day 1 to day 7 after SIM treatment, with the peak at day 7. However, the basal RSNA appears to be decreased to the same degree from day 3 to day 7 after SIM treatment. Moreover, at days 2 and 3, the basal RSNA in the SIM-treated rabbits was lower than both before SIM treatment and vehicle treatment of rabbits (Fig. 2); however, this was not the case for the arterial baroreflex (Fig. 4). Therefore, we tend to regard the SIM-induced inhibition of sympathetic activity as the cause of the SIM-induced improvement in baroreflex function. Based on these data, we believe that the critical sequences of events after SIM treatment are as follows. SIM up-regulates nNOS expression in the RVLM and then suppresses sympathetic nerve activity, which in turn improves arterial baroreflex function.

One critical question raised from the above results is how SIM up-regulates nNOS expression. Statins, including SIM, are potent inhibitors of HMG-CoA reductase and cholesterol biosynthesis and, therefore, are widely used in the treatment of hypercholesterolemia to prevent cardiovascular diseases, such as myocardial infarction, stroke, and sudden cardiac death (Maron et al., 2000; Takemoto and Liao, 2001). Recent evidence indicates that statins also benefit the cardiovascular system via cholesterol-independent effects, including the inhibition of small GTP-binding protein Rho (Liao, 2002). ROCKs were found to be one of the first downstream targets of RhoA (Leung et al., 1995; Matsui et al., 1996; Ishizaki et al., 1996). In endothelial cells, statin-induced inhibition of RhoA geranylgeranylation decreases membrane GTP-bound active RhoA and subsequent ROCK activity, leading to the up-regulation of eNOS (Laufs and Liao, 1998). Therefore, we hypothesized that the same intracellular signaling pathway might also mediate the SIM-induced up-regulation of nNOS in neurons and observed the effects of exogenous isoprenoid intermediates on the SIM-induced overexpression of nNOS mRNA in CATH.a neurons. As was shown in Fig. 6, the up-regulation of nNOS mRNA expression by SIM treatment was completely abolished by the L-mevalonate, FPP, and GGPP. These results suggest that the up-regulation of nNOS by SIM appears to be specific to the inhibition of HMG-CoA reductase, because the addition of mevalonate and its downstream products completely abolish the stimulatory effect of SIM on nNOS expression. Recently, Nakata et al. (2007) demonstrated that, in cultured rat aortic smooth muscle cells, treatment with atorvastatin significantly increased nNOS mRNA and protein expression through the activation of the Akt/nuclear factor-κB pathway. It is not known whether this pathway also mediates the SIM-induced up-regulation of nNOS mRNA expression observed in the current experiment. However, the time course of atorvastatin-induced nNOS expression in smooth muscle cells is almost exactly the same as that of SIM-induced nNOS expression in CATH.a cells, with the initial increase in nNOS expression at day 1 and the peak effect at day 2 implying a potential common intracellular signaling pathway mediating the

---

**Fig. 4.** Group data showing the time course of intracerebroventricular infusion of SIM-induced increase in the arterial baroreflex function and the blockade of L-NAME on this SIM effect. *, P < 0.05 compared with vehicle group; #, P < 0.05 compared with pre-SIM treatment in the same group; @, P < 0.05 compared with SIM group. n = 7 in SIM group; n = 6 in vehicle group; n = 6 in SIM + Y-27632 group.

**Fig. 5.** Western blot analysis for protein expression of nNOS in the RVLM. Top, representative Western blots showing the up-regulation of nNOS protein expression in the RVLM of a SIM-treated CHF rabbit compared with a vehicle-treated CHF rabbit. Bottom, results of densitometric analysis representing means ± S.E. *, P < 0.05 compared with vehicle group.

**Fig. 6.** Real-time RT-PCR analysis for mRNA expression of nNOS in the CATH.a neuronal cell line. *, P < 0.05 compared with vehicle group; #, P < 0.05 compared with SIM group. n = 4.
stain-induced up-regulation of nNOS in smooth muscle cells and neurons.

In conclusion, we demonstrated that centrally administered SIM decreased RSNA and improved arterial baroreflex function via up-regulation of nNOS expression in the RVLM of CHF rabbits. We further documented that the inhibition of HMG-CoA reductase and its downstream pathway mediated the up-regulation of nNOS by SIM, in which the RhoA/ROCK pathway plays a role.

Acknowledgments

We acknowledge the expert technical assistance of Pamela Curry, Johnnie F. Hackley, Kaye Talbitzer, Phyllis Anding, and Li Yu.

References


In conclusion, we demonstrated that centrally administered SIM decreased RSNA and improved arterial baroreflex function via up-regulation of nNOS expression in the RVLM of CHF rabbits. We further documented that the inhibition of HMG-CoA reductase and its downstream pathway mediated the up-regulation of nNOS by SIM, in which the RhoA/ROCK pathway plays a role.

Acknowledgments

We acknowledge the expert technical assistance of Pamela Curry, Johnnie F. Hackley, Kaye Talbitzer, Phyllis Anding, and Li Yu.

References


