Rosuvastatin improves cerebrovascular function in Zucker obese rats by inhibiting NAD(P)H oxidase-dependent superoxide production

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Rosuvastatin improves cerebrovascular function in Zucker obese rats by inhibiting NAD(P)H oxidase-dependent superoxide production. Am J Physiol Heart Circ Physiol 290: H1264–H1270, 2006. First published November 11, 2005; doi:10.1152/ajpheart.00804.2005.—Insulin-resistance induces cerebrovascular dysfunction and increases the risk for stroke. We investigated whether rosuvastatin (RSV), a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, can reverse reduced cerebrovascular responsiveness in insulin-resistant rats. Dilator responses of the basilar artery (BA) were examined after 1-day or 4-wk RSV (2 mg·kg−1·day−1) treatment in anesthetized 12-wk-old insulin-resistant Zucker obese (ZO) and lean (ZL) rats by using a cranial window preparation. Vehicle-treated ZO rats had significantly higher fasting insulin, total cholesterol (TC), and triglyceride (TG) levels compared with ZL rats. In addition, in the ZO rats, dilator responses of the BA to acetylcholine, loprost, cromakalim, and potassium chloride were significantly reduced when compared with ZL rats. One-day RSV treatment improved dilator responses of the ZO BAs without altering lipid levels. Four-week RSV treatment lowered both TC and TG by 30% and also improved dilator responses of the ZO BAs, although without additional effects compared with the 1-day RSV treatment. NAD(P)H oxidase-dependent superoxide production was significantly higher in the cerebral arteries of vehicle-treated ZO rats compared with ZL rats, but both 1-day and 4-wk RSV treatments normalized elevated superoxide levels in the ZO arteries. These findings demonstrate that RSV improves cerebrovascular function in insulin-resistance independently from its lipid-lowering effect by the inhibition of NAD(P)H oxidase.

cerebral circulation; statins; nitric oxide; potassium channels; diabetes mellitus

INSULIN RESISTANCE (IR) increases the prevalence of cerebrovascular events, and IR patients with stroke are subject to more severe progression, slower recovery, and higher mortality (17, 27, 33). In the elderly, IR is also a risk factor for dementia, particularly Alzheimer’s disease (40). One possible link between IR and the increased risk for these diseases is the cerebrovascular dysfunction induced by IR. Previous studies have indicated that dilator responses of cerebral arteries mediated by endogenous nitric oxide (NO) and activation of vascular smooth muscle K+ channels are impaired in IR animals (7–10). These alterations in cerebrovascular function are mediated by protein kinase C and oxidative stress, and diminished dilator responses can be restored by acute topical treatments of PKC inhibitors and/or scavengers of reactive oxygen species (9, 10).

Currently, there are no specific treatments for the IR-induced cerebrovascular dysfunction; however, statins, a relatively new class of lipid-lowering agents, could provide a novel therapeutic approach. These agents lower lipid levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, and are known to reduce cardiovascular morbidity and mortality in diabetic patients (13, 14). Statins improve cardiovascular function in IR both indirectly via effects on blood elements such as triglycerides, cholesterol, and low-density lipoproteins (5, 28) and by direct effects on the vasculature. These direct effects include the facilitation of endothelial nitric oxide (NO) production (12, 16, 41) and reduction of oxidative stress in the vessel wall (25, 34, 39). Although improvement of peripheral vascular function by statins is well documented, data concerning the effects of statins on the cerebral circulation are limited. It has been shown that long-term statin treatment increases endothelial NO synthase (eNOS) expression, and NO-mediated elevation of cerebral blood flow in healthy animals (42) reduces infarct size after middle cerebral artery occlusion (1, 21) and ameliorates cerebral vasospasm after subarachnoid hemorrhage (26); however, there are no studies that investigate whether statin treatment improves IR-induced cerebrovascular dysfunction.

In this study we examined the effects of rosuvastatin (RSV), a new hydrophilic statin, on the cerebrovascular function of IR Zucker obese (ZO) and lean (ZL) rats. We used chronic (4 wk) as well as acute (1 day) RSV treatments to reveal whether lowered lipid levels are required for the beneficial effects of RSV. We assessed dilator responses of the basilar artery (BA) mediated by acetylcholine, NO, prostacyclin, and vascular smooth muscle (VSM) K+ channels, because earlier studies indicated the impairment of these vasoregulatory pathways in IR (7–10). In addition, we tested whether changes in cerebrovascular function after RSV treatment are associated with inhibition of NAD(P)H oxidase and diminished superoxide anion (O2−) production in the cerebral arteries and whether RSV treatment has any effect on the expression of NAD(P)H oxidase subunits or eNOS.

MATERIALS AND METHODS

Experimental groups. The experimental protocol was approved by the Animal Care and Use Committee at Wake Forest University
Health Sciences (Winston-Salem, NC). Twelve-week-old male ZL (n = 11) and ZO (n = 12) rats (Harlan, Indianapolis, IN) were treated once, 24 h before the experiments, with either saline (0.3 ml sc) or RSV (2 mg/kg sc in 0.3 ml saline), and 8-wk-old male ZL (n = 12) and ZO (n = 12) rats were treated for 4 wk with either saline (0.3 ml sc/day) or with RSV (2 mg/kg sc in 0.3 ml saline/day). The last treatments were given 24 h before the experiments. As described previously (10), body weight, blood pressure, fasting glucose, total cholesterol, triglyceride, and insulin levels were measured to characterize IR in the ZO rats and to assess metabolic effects of RSV. Because there was no difference in the vascular reactivity and metabolic state of the rats treated with saline for either 1 day or for 4 wk, we combined the data acquired from these groups.

Measurements of vascular responses. Rats in a fasting state were anesthetized with pentobarbital sodium (70–80 mg/kg ip, supplemented with 10–20 mg·kg⁻¹·h⁻¹ iv) and were ventilated through the trachea with a mixture of room air and O₂. Depth of anesthesia was monitored regularly by applying pressure to a paw. If changes in heart rate or blood pressure were observed, additional pentobarbital sodium was administered. Catheters were placed in the femoral artery and vein to measure arterial blood pressure, to obtain arterial blood samples, and to infuse supplemental anesthetics. Arterial blood gases were kept within the physiological range throughout the experiments.

A ventral craniotomy was performed over the brainstem (11), and the cranial window was superfused with artificial cerebrospinal fluid (CSF) at a rate of 3 ml/min. The artificial CSF (in mmol/l: 2.95 KCl, 132 NaCl, 3.69 dextrose, 1.7 CaCl₂, 0.64 MgCl₂, and 23.2 NaHCO₃) was bubbled with 5% CO₂ in N₂ and maintained at 37–38°C. The gas tensions of the CSF were kept within physiological ranges. Changes in diameter of the BA were observed by a surgical microscope equipped with a CCD camera connected to a PC and analyzed by using the Scion Image Software (Scion, Frederick, MD).

Concentration-dependent dilator responses were evaluated in response to topical application of acetylcholine, iloprost, cromakalim, and to elevations of K⁺ concentration in the CSF. Drugs were dissolved in CSF, except for cromakalim, which was dissolved in DMSO and CSF. The same concentration of DMSO alone had no effect on vessel diameter. The magnitudes of vascular responses were calculated as percentage of baseline diameter measured for 1 min immediately before the drug applications. At the end of each study, animals were euthanized by an overdose of pentobarbital sodium.

Detection of O₂⁻ production. O₂⁻ production was measured with lucigenin-enhanced chemiluminescence assay. Cerebral arteries from ZL and ZO rats were dissected simultaneously and placed in a luminometer (BMG Fluostar Optima) in 37°C phosphate-buffered saline. Scintillation counts were obtained in the presence of lucigenin (5 μmol/l), and background-corrected values were normalized to protein content. After 30 min incubation, baseline scintillation was recorded for 10 min. NADPH (10⁻²–10⁻⁶ mol/l) was then added into the incubating solution with or without the NAD(P)H oxidase inhibitor apocynin (3 × 10⁻⁴ mol/l), and scintillation was recorded for 20 min at each NADPH concentration.

RT-PCR. Total RNA was obtained from isolated cerebral arteries, including the BA, and the anterior, middle, and posterior cerebral arteries by using the RNaseasy Fibrous Tissue Mini Kit (Qiagen, Valencia, CA). RT-PCR experiments were carried out using the OneStep RT-PCR Kit (Qiagen) according to the manufacturer’s instructions. The conditions for each RT-PCR were optimized for linearity. mRNA levels of the NAD(P)H oxidase subunits (gp91phox, NOX-1, NOX-4, p22phox, p47phox, p67phox), as well as eNOS, were analyzed using specific primers (Table 1).

Chemicals. RSV was received from AstraZeneca (Macclesfield, UK). Acetylcholine, lucigenin, and apocynin were purchased from Sigma (St. Louis, MO). Cromakalim was obtained from Tocris (Ellisville, MO), and iloprost was from Schering (Berlin, Germany).

Statistical analysis. All data are expressed as means ± SE. Effects of treatments and differences between ZL and ZO rats were evaluated using analysis of variance, followed by Tukey’s post hoc test. The criterion for significance was P < 0.05.

RESULTS
IR in the ZO rats, metabolic effects of RSV. ZO rats were significantly heavier than ZL rats (510 ± 5 vs. 328 ± 9 g, respectively, P < 0.01); however, RSV had no effect on body weight. Mean arterial blood pressure and fasting glucose levels were similar in the ZL (106 ± 1 mmHg and 87 ± 6 mg/dl) and ZO (109 ± 4 mmHg and 92 ± 8 mg/dl) rats, and neither 1-day nor 4-wk RSV treatment changed these parameters. Insulin was markedly elevated in the saline-treated ZO rats compared with ZL rats (16 ± 1 vs. 1 ± 0.1 ng/dl, P < 0.01), and 1-day and 4-wk RSV treatments did not affect blood insulin levels in the ZL rats or reduce the hyperinsulinemia in the ZO rats. Total cholesterol and triglyceride levels were significantly elevated in the saline-treated ZO group, and whereas 1-day RSV did not change these parameters, 4-wk RSV treatment significantly reduced both total cholesterol and triglyceride levels (Fig. 1).

Effects of RSV on vascular reactivity. Resting diameter of the BA was similar in all experimental groups: saline-treated ZL and ZO rats were 267 ± 4 (n = 9) and 264 ± 5 μm (n = 9), respectively; 1-day RSV-treated ZL and ZO rats were 257 ± 5 (n = 6) and 256 ± 2 μm (n = 7), respectively; and 4-wk RSV-treated ZL and ZO rats were 260 ± 6 (n = 8) and 258 ± 5 μm (n = 8), respectively.

Acetylcholine-induced dose-dependent relaxations in the BAs were significantly reduced in the saline-treated ZO rats compared with ZL rats (Fig. 2A). One-day RSV treatment improved acetylcholine-induced dilation significantly in the ZO rats but had no effect in the ZL group. Four-week RSV treatment also improved relaxation to acetylcholine in the ZO rats, although without additional effects compared with 1-day treatment. Four-week RSV slightly augmented responses in the ZL group, too, but only at 10⁻⁶ mol/l concentration of acetylcholine (Fig. 2A).

Relaxation to iloprost was significantly reduced in salinetreated ZO rats compared with ZL rats (Fig. 2B). One-day RSV markedly improved iloprost-induced relaxation in the ZO rats, whereas it had only a minor, but significant, effect in the ZL group, so that the difference diminished between ZL and ZO rats. Four-week RSV also augmented iloprost-induced re-

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### Table 1. Sequences of oligonucleotide primers for RT-PCR

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer Sequences</th>
<th>No. of Cycles</th>
<th>PCR Product bp</th>
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<tr>
<td>NOX-1</td>
<td>5'-ATTCCAGATGATGAAAGCCG-3'</td>
<td>45</td>
<td>534</td>
</tr>
<tr>
<td>NOX-4</td>
<td>5'-TCACGTAGACGCTGTACCTTT-3'</td>
<td>45</td>
<td>443</td>
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<td>gp91phox</td>
<td>5'-CTCATGATTTGGAAGATTGTAT-3'</td>
<td>35</td>
<td>537</td>
</tr>
<tr>
<td>p22phox</td>
<td>5'-GGATGTCATCCTGCTGCTG-3'</td>
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<td>306</td>
</tr>
<tr>
<td>p47phox</td>
<td>5'-GCGAAGAGCTTGAGAATACCC-3'</td>
<td>33</td>
<td>415</td>
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<tr>
<td>p67phox</td>
<td>5'-ATATCGCCCTTTCTGACCAACC-3'</td>
<td>33</td>
<td>444</td>
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<tr>
<td>eNOS</td>
<td>5'-GACTGGATTGACCACCTCCTCGG-3'</td>
<td>28</td>
<td>353</td>
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</tbody>
</table>

**eNOS**, endothelial nitric oxide synthase.
Cromakalim-induced relaxation was significantly diminished in the saline-treated ZO rats compared with ZL rats. One-day RSV improved relaxation in the ZO rats, whereas it had no effect in the ZL rats. Four-week RSV also enhanced cromakalim-induced dilation in the ZO group, although without additional effect compared with 1-day RSV (Fig. 3 B).

Relaxation to elevations in the K⁺ concentration of the CSF was significantly reduced in the saline-treated ZO rats compared with ZL rats (Fig. 3 B). After only 1-day RSV treatment, however, NADPH-induced O₂⁻ production was reduced to normal levels. Four-week RSV had an even more significant effect on O₂⁻ production, and reduced NADPH induced chemiluminescence in both the ZL and ZO groups compared with saline-treated ZL rats (Fig. 4 B).
nor 4-wk RSV treatments reduced the mRNA expression of NAD(P)H oxidase subunits. On the contrary, the mRNA level of p22phox became significantly elevated after 4-wk RSV treatment in both the ZL and ZO samples by about 27% and 28%, respectively (ZL: from 1.13 ± 0.07 to 1.45 ± 0.07 vs. ZO: from 1.09 ± 0.07 to 1.46 ± 0.10; p22/β-actin mRNA, n = 6 in each group).

eNOS mRNA levels were 20% higher in cerebral arteries isolated from saline-treated ZO rats compared with ZL rats (2.74 ± 0.09 vs. 2.29 ± 0.04 eNOS/β-actin mRNA, n = 6 in each group). However, RSV treatment had no detectable effect on eNOS levels in either the ZL or the ZO rats (Fig. 5).

**DISCUSSION**

The major findings of this study are that both acute and long-term RSV treatments restore dilator responses of the BA mediated by NO, prostacyclin, and VSM K⁺ channels in IR ZO rats. These effects of RSV are independent from changes in plasma lipid levels and may be mediated by the inhibition of NAD(P)H oxidase and reduced oxidative stress. However, diminished NAD(P)H oxidase-dependent O₂⁻ production is not associated with a decrease in mRNA expression of the subunits of the enzyme or a change in eNOS levels.

Previous in vitro and in vivo studies using dietary (7–9) and genetic (10) models of IR have demonstrated that cerebrovascular dilator responses are reduced in the IR rats compared with their non-IR counterparts. For example, in the ZO rats, acetylcholine-induced relaxation is impaired due to altered endothelial NO signaling, whereas iloprost-induced relaxation is diminished due to a dysfunction of the large conductance Ca²⁺-activated K⁺ channels. In addition, ATP-dependent and inwardly rectifier K⁺ channel-mediated dilator responses are also reduced in the ZO rats compared with ZL rats (10). The implication of these findings is that cerebral resistance vessels are not able to respond normally to a variety of endogenous metabolic stimuli, which could lead to a mismatch between blood flow and metabolic rate. The resulting chronic hypoperfusion of the brain might contribute to the development of general dementia and Alzheimer’s disease (40), and the reduced dilator ability of the cerebral arteries may increase neurological consequences and mortality due to occlusive events and hemorrhagic strokes by preventing appropriate compensatory responses in collateral arteries (17, 27, 33).

We have also demonstrated that increased O₂⁻ production is a major cause of cerebrovascular impairment in the IR state and that dilator responses can be restored to normal in IR...
animals by scavenging reactive oxygen species (9, 10). Studies in the peripheral circulation showed a similar role for increased O$_2^-$ production in IR-induced dysfunction in other vascular beds (4, 18, 19, 32, 35). Elevated O$_2^-$ levels are responsible for reduced bioavailability of NO partly because O$_2^-$ scavenges NO-forming peroxynitrate and partly due to uncoupling of eNOS caused by the oxidation of the tetra-hydrobiopterin cofactor of the enzyme (22, 32). In addition, O$_2^-$ has also been shown to inhibit K$^+$ channel function in various pathological conditions (2, 23), and it seems that O$_2^-$ production in IR and diabetes is elevated in all layers of the vascular wall, including VSM cells (10, 24). Whereas the major vascular source of O$_2^-$ in IR and diabetes is the NAD(P)H oxidase (4, 15, 35), the concomitant uncoupling of eNOS may augment oxidative stress in the endothelium (22, 32).

HMG-CoA reductase inhibitors represent an ideal class of agents for the treatment of IR-induced vascular dysfunction. Statins are known to lower cardiovascular morbidity and mortality in diabetic patients (13, 14) and have been shown to have both direct and indirect effects on vascular function. Indirectly, they improve cardiovascular outcomes through their ability to normalize lipid profiles. For example, by lowering membrane cholesterol levels, statins restore normal cell membrane structure and normal membrane protein function in endothelial cells (25, 38). In addition, by reducing the serum concentration of LDL, they also lower the amount of oxidized LDL, a key initiator in vascular dysfunction (31, 36). Direct vascular effects of statins, independent of serum lipid levels, involve the inhibition of inflammatory responses (20, 29) and NAD(P)H oxidize-dependent O$_2^-$ production, as well as improvement of antioxidant capacity (37, 39). Augmentation of endothelial NO production is due partly to reduced oxidative stress but also to the upregulation of eNOS (1, 21).

In the present study, we showed for the first time that similarly to peripheral vascular beds, statin treatment improves the function of cerebral arteries in IR animals. We assessed dilator responses of the BA elicited by acetylcholine, iloprost, cromakalim, and extracellular K$^+$ because these regulatory pathways represent some of the most important dilator mechanisms in the cerebral circulation and RSV treatment improved dilator function mediated by all examined regulatory pathways. The improvement in cerebrovascular function after RSV treatment is independent of changes in plasma lipid levels, because 1-day RSV treatment, which had no effect on total cholesterol and triglyceride concentrations, and 4-wk RSV treatment, which reduced plasma lipid levels by about 30%, improved BA function similarly. Interestingly, RSV augmented some of the dilator responses even in the ZL rats, but generally to a much lesser extent, so the differences between the ZL and ZO rats diminished after RSV treatment. However, we cannot preclude RSV as having a general effect in increasing cerebrovascular dilator responses to all stimuli.

Because the cerebrovascular effects of RSV resembled that of superoxide dismutase applied topically (10), we hypothesized that RSV may reduce O$_2^-$ levels in the cerebral arteries as well. Using lucigenin-enhanced chemiluminescence, we found that elevated baseline O$_2^-$ formation in the cerebral arteries of ZO rats is lowered after both 1-day and 4-wk RSV treatments. In addition, elevated O$_2^-$ levels were also normalized in the ZO arteries with apocynin, a selective inhibitor of NAD(P)H oxidase, indicating that elevated basal O$_2^-$ production in the ZO arteries was due to increased activity of NAD(P)H oxidase and that RSV may have inhibited this source of O$_2^-$ However, we do not have data concerning acute effects of selective inhibitors of NAD(P)H oxidase on cerebrovascular responses in ZO arteries. Therefore, whereas our data strongly suggest a link between increased activity of NAD(P)H oxidase and O$_2^-$-mediated inhibition of dilator responses, we cannot make a definitive statement concerning this relationship. On the other hand, an inhibitory effect of RSV on NAD(P)H oxidase was further supported by the findings that NADPH-induced O$_2^-$ production that was elevated in the saline-treated ZO arteries was significantly reduced by both 1-day and 4-wk RSV treatments. It has been shown previously that application of NADH or NADPH in similar experimental conditions increases O$_2^-$ formation in intact BAs, which is inhibited by the blockade of NAD(P)H oxidase (6). It is also important to note that NADPH-induced increase in O$_2^-$ production was inhibited by 4-wk RSV treatment in the ZL arteries, too. This indicates that RSV might have effects on O$_2^-$ production even if it is undetectable with our methods during baseline conditions, and it can also explain why certain dilator responses are augmented in ZL BAs. For example, similar increases in dilator responses were observed in control animals even after topical application of SOD (10) or SOD + catalase (9), indicating that O$_2^-$ may have a role in the regulation of cerebrovascular responses even under physiological conditions.

There are several possible ways by which statins can reduce oxidative stress in the vessel walls. In peripheral arteries, mRNA expressions of NAD(P)H oxidase subunits were reduced by long-term RSV (3, 30) and atorvastatin (39) treatments, and statins also inhibit membrane translocation of rac1 GTPase, which is required for the activation of NAD(P)H oxidase (39). Because of the small amount of tissue available from the cerebral arteries, we were only able to study mRNA expressions of NAD(P)H oxidase subunits using RT-PCR. We measured mRNA levels of the membrane-bound gp91phox, NOX-1, NOX-4, p22phox, and the cytosolic p47phox and p67phox subunits of NAD(P)H oxidase. With the exception of NOX-1, we were able to detect all these subunits in the cerebral arteries, but we were only able to detect gp91phox and NOX-1 in ZL BAs. For example, similar increases in dilator responses were observed in control animals even after topical application of SOD (10) or SOD + catalase (9), indicating that O$_2^-$ may have a role in the regulation of cerebrovascular responses even under physiological conditions.
cerebral arteries of ZL and ZO rats; however, only NOX-4 showed a relatively small increase in the saline-treated ZO rats compared with ZL rats. Although after 4-wk RSV treatment, this difference in NOX-4 mRNA levels diminished between the ZL and ZO groups, compared with the vehicle-treated groups, and RSV did not significantly alter the expression of this subunit. In contrast, mRNA of the p22phox subunit was elevated significantly in response to 4-wk RSV treatment in both the ZL and ZO rats, however, without a significant difference between the two groups. Although small changes in mRNA expression can remain undetected by RT-PCR, these findings suggest that the beneficial effects of RSV on cerebrovascular function are not mediated by an inhibition of NAD(P)H oxidase subunit transcription.

Upregulation of eNOS is considered a major effect of statins on the vasculature in both the peripheral and cerebral circulations (1, 16, 21, 41, 42). However, our previous findings that eNOS is upregulated in the ZO cerebral arteries (10) have suggested that this mechanism may not be important in the treatment of IR-induced cerebrovascular impairment. It appears that upregulation of eNOS in certain pathological conditions accompanied by oxidative stress is a compensatory mechanism which, due to the uncoupling of the enzyme, results in elevated O$_2^–$ formation rather than increased NO levels (22). Therefore, upregulation of eNOS by RSV in the cerebral arteries of ZO rats without reducing oxidative stress would only further stimulate O$_2^–$ production. Indeed, we found that expression of eNOS was elevated in all ZO groups compared with ZL rats, and RSV treatment had no apparent effect on eNOS mRNA levels in either the ZL or in the ZO rats. Thus, although further investigation is needed to determine why RSV has no effect on eNOS expression in this animal model, it seems that NO-mediated relaxation in the IR cerebral arteries is improved mainly by the inhibition of O$_2^–$ production rather than by the upregulation of eNOS.

In conclusion, the present data reveal that a new HMG-CoA reductase inhibitor RSV inhibits NAD(P)H oxidase-dependent O$_2^–$ production and restores normal cerebrovascular function in IR ZO rats. These effects appear to be independent of changes in plasma lipid concentrations and were observed as early as 1 day after treatment. Our findings provide evidence regarding the direct vascular effect of RSV and further emphasize the importance of oxidative stress in the pathomechanism of IR-induced cerebrovascular dysfunction. It seems likely that statins such as rosvastatin will prove to be useful in the prevention and treatment of cerebrovascular diseases in IR patients.

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CEREBROVASCULAR EFFECTS OF ROSUVASTATIN


