Clinical and Experimental Health Sciences

Relaxant Effect of Rosuvastatin in Isolated Rat Aorta with Perivascular Adipose Tissue

Deniz Kaleli Durman[1], G. Ruveyda Aktaş[1,2], Meryem Aras[1,2,3], B. Sönmez Uydeş Doğan[1]

[1] Istanbul University, Faculty of Pharmacy, Department of Pharmacology, İstanbul, Türkiye.
[2] Istanbul University, Graduate School of Health Sciences, İstanbul, Türkiye.
[3] Biruni University, Faculty of Pharmacy, Department of Pharmacology, İstanbul, Türkiye.

Correspondence Author: Deniz Kaleli Durman
E-mail: deniz.kaleli@istanbul.edu.tr

Received: 05.10.2024 **Accepted:** 14.12.2024

ABSTRACT

Objective: Rosuvastatin displays favorable pleiotropic effects on vascular system to reduce the risk of cardiovascular events besides providing an intensive reduction in LDL-C levels. The role of perivascular adipose tissue (PVAT) in modulating the vasorelaxant effect of rosuvastatin is not evaluated so far. The present study aimed to investigate the vascular relaxant effect of rosuvastatin in rat aortic rings with intact PVAT, as well as to evaluate the possible mechanisms underlying this effect in relation to nitric oxide (NO) and prostaglandin pathways.

Methods: Thoracic aorta rings with intact PVAT, isolated from male Wistar rats (n=5), were mounted on an isolated organ bath system. Endothelium-dependent responses to acetylcholine (Ach,10^{-6}-10^{-4}M) were obtained in aortic rings precontracted submaximally with phenylephrine (Phe,10^{-6}-3x10^{5}M). The concentration-dependent relaxant effect of rosuvastatin (10^{-7}-10^{-4}M) was examined in the absence and presence of NO inhibitor, L-NOARG (10^{-4}M, 30min.) and cyclooxygenase inhibitor, indomethacin (10^{-5}M, 30min.). Vascular relaxation capacity of aortic rings was checked by the nitrovasodilator, sodium nitroprusside (SNP,10^{-6} M) at the end of the experiments.

Results: Rosuvastatin (10^{-7}-10^{-4}M) produced concentration-dependent relaxations in Phe-precontracted rat aortic rings with intact PVAT. Pretreatment with L-NOARG significantly attenuated the relaxant responses to rosuvastatin in isolated rat aortic rings with intact PVAT. However, pretreatment with indomethacin did not modify the relaxations to rosuvastatin. In the aortic rings, maximal relaxation responses to Ach and SNP were determined to be 75.87±2.68% and 102.54±2.92%, respectively.

Conclusions: This study will provide a basis for investigating the interaction between PVAT and statins in vascular homeostasis.

Keywords: Rosuvastatin Calcium, Perivascular adipose tissue, Vasodilation, Nitroarginine, Indomethacin

1. INTRODUCTION

Statins, which play a crucial role in both the prevention and treatment of atherosclerotic cardiovascular diseases, are primarily recognized for their lipid-lowering effects. However, research has shown that statins also exert a variety of pleiotropic effects on the vascular system, including anti-inflammatory, antioxidant, and antithrombotic properties, independent of their lipid-lowering mechanisms (1-5). Additionally, several in vitro studies have reported relaxant effects of statins on vascular and non-vascular preparations (6-17). These findings suggest that statins not only reduce lipid levels but also have broader biological effects on vascular function, highlighting their therapeutic potential beyond cholesterol reduction.

Rosuvastatin is one of the most clinically preferred and potent statins with a long half-life (18-20). Its acute vasorelaxing effects have been demonstrated in various isolated vascular and non-vascular preparations, primarily through the inhibition of spasmogen-induced contractions (9,10,15,16,17,21). Moreover, with the increasing recognition of perivascular adipose tissue (PVAT) as a key player in vascular function, the potential PVAT-mediated effects of statins have become an intriguing area of research (22). PVAT, which surrounds blood vessels, plays a central role in maintaining vascular homeostasis via releasing various vasoactive substances and displaying an anticontractile effect (23-25). A previous in vivo study demonstrated that treatment with atorvastatin, but not pravastatin, augmented the anticontractile effect of PVAT most likely via H_2S and K_{ATP} channel-dependent manner (26). However, the possible influence of PVAT on the vasorelaxant effect of other statins

DOI: 10.33808/clinexphealthsci.1561664

as well as other mechanisms such as nitric oxide (NO) and prostaglandin pathways remains unclear.

In this study, we aimed to investigate the vascular relaxant effect of rosuvastatin on rat aortic rings with intact PVAT, as well as to evaluate the possible mechanisms underlying this effect in relation to NO and prostaglandin pathways. For this purpose, the concentration-dependent relaxant effect of rosuvastatin was examined in isolated rat thoracic aorta with intact PVAT in the absence and presence of NO inhibitor, L-NOARG and cyclooxygenase inhibitor, indomethacin.

2. METHODS

2.1. Animals and Preparation of Aortic Rings

Male Wistar Albino rats (8-10 weeks old, ~250 g) were obtained from Istanbul University, Aziz Sancar Institute of Medical Sciences, Experimental Animals Laboratory (DETAE) and housed under standard laboratory conditions (21±2°C, 45–65% relative humidity, 12h light/dark cycle, with ad libitum access to food and water). All procedures were carried out in the Experimental Animal Care and Research Unit of Istanbul University Faculty of Pharmacy (EDEHAB), according to the approval of the Local Ethics Committee of Animal Experiments of Istanbul University (IU-HADYEK) (22/11/2023, No:2267678). The Arrive Guidelines 2.0. was followed in all procedures (27).

After one week of acclimatization, the rats (n=5) were anesthetized via intraperitoneal injection (i.p.) of ketamine/xylazine (100 mg/kg /10mg/kg) and the thoracic aortas were immediately excised and placed in Krebs Ringer-bicarbonate solution of the following composition (mM): NaCl 118, KCl 4.7, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4.7H_2O$ 1.2, $CaCl_2$ 2.5, glucose 10 and disodium EDTA 0.026. Isolated thoracic aorta was divided into four rings 3-4mm, and PVAT was left intact. Then isolated rat aortic rings were immediately transferred to the laboratory for studying vascular reactivity in the isolated organ bath system, with each ring assigned to a different experimental protocol.

Isolated rat aortic rings with intact PVAT were mounted between two stainless steel L-shaped hooks in 10mL jacketed organ baths containing Krebs-Ringer bicarbonate solution, maintained at 37°C, and aerated with a mixture of 95% O_2 and 5% CO_2. One hook was fixed at the base of the organ bath, while the other was attached to a force-displacement transducer (Grass Model FT03; Grass Telefactor, West Warwick, RI). The contractile responses were recorded using a computer-controlled polygraph system (PowerLab-ADInstruments, Oxford, UK). The isolated organ bath experiments were conducted as described previously (8).

2.2. Vascular Experiments

Briefly, the aortic rings were equilibrated for 1 hour under a resting tension of 1g. Subsequently, two consecutive contractions were induced using 40mM potassium chloride (KCl) to standardize the aortic rings, and preparations that produced a contraction of less than 0.5g were discarded. The functional integrity of the endothelium was assessed by the cumulative administration of acetylcholine (Ach, 10^{-6}-10^{-4}M), an endothelium-dependent vasodilator, to aortic rings submaximally precontracted by the selective α1-adrenergic agonist, phenylephrine (Phe, 10^{-6}-$3x10^{-5}$M). The vasorelaxant capacity of the aortic rings was further evaluated by the administration of sodium nitroprusside (SNP, 10^{-6}M), a directly-acting nitrovasodilator, at the end of each experiment.

The experimental protocol aimed to investigate the vascular effects of rosuvastatin on rat aortic rings with intact PVAT, which had been precontracted submaximally (70–80% of maximal contraction) with Phe (10^{-6}-$3x10^{-5}$M). When Phe-induced contractions had reached a stable plateau, rosuvastatin was applied cumulatively at increasing concentrations (10^{-7}-10^{-4}M). To examine the role of vasodilator factors namely NO and prostaglandins, the effects of rosuvastatin were evaluated after pre-incubation of the aortic rings with NO synthase inhibitor, L-NOARG (10^{-4}M) and the cyclooxygenase inhibitor, indomethacin (10^{-5}M) respectively, for 30min. In order to analyse the possible effect of the vehicle for rosuvastatin, cumulative application of DMSO was provided. Additionally, in the preliminary experiments time-matched control group was performed in order to confirm that the precontractions induced by Phe remained stable for the experimental period.

2.3. Statistical Analyses

Values are presented as mean ± S.E.M. In all experiments, "n" refers to the number of rats from which the aortas were isolated. The relaxant responses to Ach, SNP and rosuvastatin are expressed as the percentage of Phe-induced precontraction in that vessel ring. The sensitivity of aortic rings to rosuvastatin is given as the effective concentration required to produce 50% of the maximal response (EC_{50}), which was calculated for each concentration-response curve by using probit analysis. Maximal relaxation responses are shown as E_{max} (%), while EC_{50} values are expressed as-log M (pEC_{50}). Data distribution for normality was checked and statistical analyses were performed by using one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test. A p-value < .05 was considered statistically significant. Statistical analyses were performed by using GraphPad® Prism version 9.4.0. for Windows (GraphPad® Software, Boston, Massachusetts USA).

2.4. Drugs and Chemicals

All drugs used were purchased from Sigma Chemical Co, USA. Rosuvastatin calcium was donated by World Medicine (Türkiye). Rosuvastatin was dissolved in DMSO and final concentration of DMSO did not exceed 0.1% in the organ bath. Indomethacin was prepared in 5% (w/v) in sodium bicarbonate and all other drugs in distilled water.

3. RESULTS

3.1. Endothelium-Dependent and – Independent Relaxant Responses

Endothelium-dependent vasodilator Ach (10^{-7}-10^{-4}M) produced concentration-dependent relaxations on isolated rat aortic rings with intact PVAT (Figure 1). The maximal relaxation response to Ach was determined to be 75.87±2.68 % (n=5). On the other hand, the directly acting endothelium-independent vasodilator SNP (10^{-6}M) produced complete relaxations in isolated rat aortic rings with intact PVAT (102.54±2.92%, n=5).

3.2. Relaxant Effect of Rosuvastatin on Isolated Rat Aorta with Intact PVAT

As shown in Figure 2, rosuvastatin (10^{-7}-10^{-4}M) induced concentration-dependent relaxations in isolated rat aortic rings with intact PVAT which were precontracted submaximally with Phe (10^{-6}-3x10^{-5}M). The vehicle administration did not produce an important influence on the precontractile tone (7.87± 3.83 %, n=4) but were significatly different from rosuvastatin (87.43±3.94 %, *p < .001, n=5) (Figure 2 and Table 1).

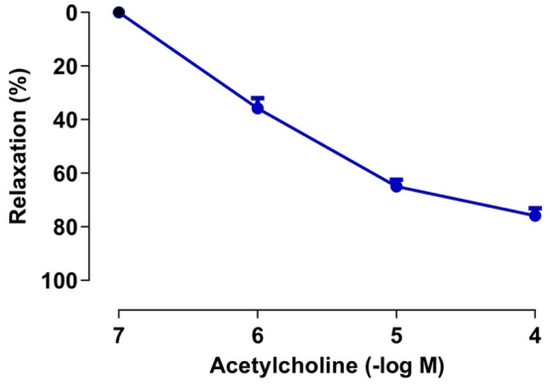

Figure 1. *Concentration-dependent relaxant effects of Acetylcholine (Ach, 10^{-7}-10^{-4}M) on isolated rat aortic rings with intact PVAT which were precontracted submaximally with Phenyleprine (Phe, 10^{-6}-3x10^{-5}M) (n=5).*

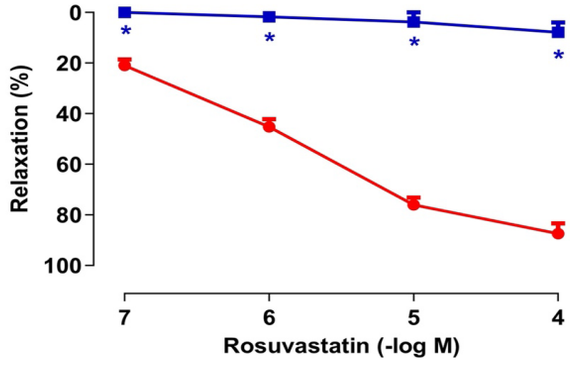

Figure 2. *Effects of rosuvastatin (10^{-7}-10^{-4} M) (•) and the vehicle, DMSO (■) on isolated rat aortic rings with intact PVAT which were precontracted submaximally with phenylephrine (Phe, 10^{-6} – 3x10^{-5}M).*p< .001 Rosuvastatin vs. DMSO, one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test, (n=4-5).*

3.3. Role of NO on the Relaxant Effect of Rosuvastatin

Pretreatment with NO synthase inhibitor, L-NOARG (10^{-4}M, 30min.) significantly attenuated the concentration-dependent relaxant responses to rosuvastatin (10^{-7}-10^{-4}M) on isolated rat aortic rings with intact PVAT (Rosuvastatin+L-NOARG *vs.* Rosuvastatin, *p < .001, n=5) (Figure 3 and Table 1). On the other hand, the relaxation response to SNP in aortic rings pretreated with NO synthase inhibitor, L-NOARG (109.60±4.06 %, n=5) was similar compared to corresponding control.

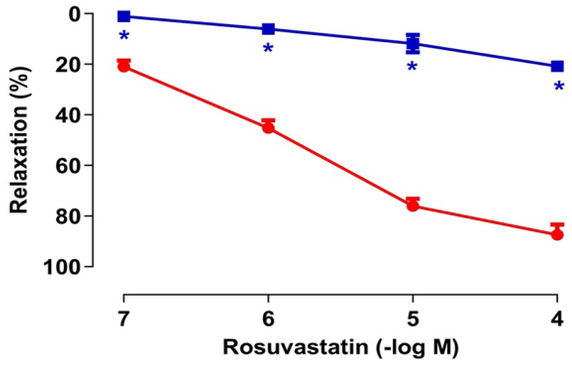

Figure 3. *Relaxant effect of rosuvastatin (10^{-7}-10^{-4} M) on isolated rat aortic rings with intact PVAT in the absence (•) and presence (■) of L-NOARG (10^{-4}M).*p< .001 Rosuvastatin+L-NOARG vs. Rosuvastatin, one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test, (n=5).*

3.4. Role of Prostaglandins on the Relaxant Effect of Rosuvastatin

Pretreatment with cyclooxygenase inhibitor, indomethacin (10^{-5}M, 30min.) did not modify the relaxation responses to rosuvastatin (10^{-7}-10^{-4} M) on isolated rat aortic rings with intact PVAT (Rosuvastatin+Indomethacin *vs.* Rosuvastatin, p> .05, n=5) (Figure 4 and Table 1). On the other hand, the relaxation response to SNP in aortic rings pretreated with cyclooxygenase inhibitor, indomethacin (87.60±8.93 %, n=5) was similar compared to corresponding control.

In order to achieve a comparable precontractile tone in rat aortic rings with PVAT, whether pretreated with inhibitors or not, the concentration of Phe (10^{-6}-3x10^{-5}M) was adjusted as appropriate (data not shown).

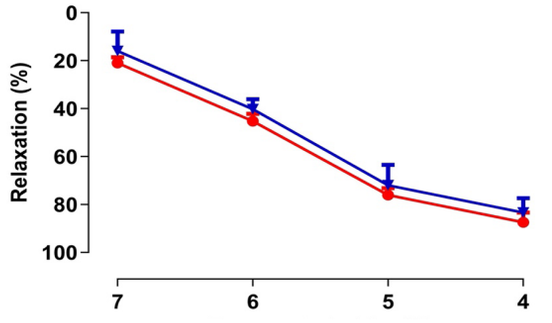

Figure 4. *Relaxant effect of rosuvastatin (10^{-7}-10^{-4} M) on isolated rat aortic rings with intact PVAT in the absence (•) and presence (■) of INDO (10^{-5}M) (p> .05, n=5).*

Table 1. *E_{max} and pEC_{50} values of rosuvastatin (10^{-7}-10^{-4}M) on phenylephrine (Phe, 10^{-6}-$3x10^{-5}$M) precontracted rat aortic rings with intact PVAT in the absence and presence of the inhibitors of NO (+L-NOARG) and prostaglandins (+INDO).*

Groups	E_{max} (%)	pEC_{50}
Rosuvastatin	87.43±3.94	5.85 ±.13
+ L-NOARG (10^{-4}M)	20.82±1.88*	5.07±.26
+ INDO (10^{-5}M)	83.35±5.88	5.90±.19

*Values are shown as mean±SEM. E_{max} values are expressed as the percentage of Phe-induced precontractions.*p< .001 Rosuvastatin+L-NOARG vs. Rosuvastatin. Statistical analyses were performed by using one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test (n=5).*

4. DISCUSSION

Rosuvastatin is one of the most clinically preferred and potent statins with various pleiotropic effects, including relaxation of vascular and nonvascular tissues (18-20). Although its vasorelaxant effect has been demonstrated in previous studies, the role of PVAT in modulating the direct vasorelaxant effect of rosuvastatin is unknown. This study demonstrated for the first time that rosuvastatin produced concentration-dependent relaxations in Phe-precontracted rat aortic rings with intact PVAT. Our findings suggest that the NO pathway, rather than the prostaglandin pathway, plays a role in the vascular relaxant effect of rosuvastatin in PVAT intact aortas.

Briefly, rosuvastatin which applied cumulatively (10^{-7}-10^{-4}M) in Phe-precontracted rat thoracic aorta with intact PVAT, produced vasorelaxation in a concentration dependent manner. This finding is in line with previous in vitro studies which demonstrated the relaxant effect of rosuvastatin in various vascular and nonvascular isolated preperations, including rat aorta, pulmonary artery and trachea (9,10,16,17). Notably, the current study demonstrated that the maximum vasorelaxation response to rosuvastatin obtained in rat aortic rings with intact PVAT is similar with the results of previous studies performed in rat aortic rings without PVAT (9,10,16,17).

On the other hand, in vivo treatment with rosuvastatin (15-20mg/kg/day) for 4-7 weeks demonstrated to restore endothelium-dependent relaxant responses to Ach in isolated aorta and electric field stimulation (EFS)-induced relaxation in corpus cavernosum obtained from Streptozotocine(STZ)-induced diabetic mice as well as diminished EFS-induced contractions in mesenteric arteries from high fat diet (HFD)-induced obese rats (21,28). The ameliorative role of rosuvastatin in NO mediated nerve and vascular function is likely to depend on the inhibiton of mevalonate pathway (21). Moreover, it has been shown that direct vasorelaxant effect of rosuvastatin in rat aorta (9,16), rat pulmonary artery (17) and calf cardiac vein (15) is partly endothelium and NO dependent. Consistent with these previous studies, our findings demonstrated that NO synthase inhibitor, L-NOARG significantly attenuated the relaxant responses to rosuvastatin in rat aortic rings with intact PVAT. Concerning that, vascular endothelium, vascular smooth muscle and PVAT are potential sources for NO (29,30), further studies will be intriguing to determine their contribution to the vasorelaxant effect of rosuvastatin in aortic rings with intact PVAT.

On the other hand, prostaglandins, particularly prostacycline, also contributes to the vasorelaxation responses of various statins, including atorvastatin, pravastatin and cerivastatin, as shown by the experiments performed in the presence of a cyclooxgenase inhibitor (8). However, present findings, in the presence of indomethacin ruled out the involvement of prostaglandins in the relaxant effect of rosuvastatin in rat aortic rings with intact PVAT, similar to a previous study in isolated rat aorta without PVAT (9). On the other hand, this finding is in contrary with a recent study conducted with rosuvastatin on isolated rat pulmonary arteries and tracheas as well as on aortic rings from rats fed with Cafeteria style (CAF) diet (10,17). This difference may be related to the presence of PVAT as well as the vascular bed and animal model studied.

PVAT plays a critical role in maintaining vascular homeostasis by releasing various bioactive molecules that can regulate vascular tone. In this respect, understanding the influence of PVAT in the vasorelaxant effect of rosuvastatin may provide a novel insight into pleitropic effects of statins through the modulation of the vascular tone to promote cardiovascular health. This study presents a potent and NO sensitive vasorelaxation profile of rosuvastatin in rat aortic rings with intact PVAT, comparable with previous studies performed in aortic preperations without PVAT. This may suggest that the relaxant effect of rosuvastatin is not modulated by PVAT. However, identifying the main source of NO in terms of vascular endothelium, vascular smooth muscle and PVAT may be a promising issue to be evaluated in future studies. As a limitation of the present the study, we examined only rosuvastatin, and thus the related findings can not be extrapolated to other statins that have different physicochemical properties.

5. CONCLUSION

Overall, the current study provides original findings regarding the vascular effects of rosuvastatin and suggests that NO, rather than prostaglandins, plays an important role in the vasorelaxation response to rosuvastatin in isolated rat aortic rings with intact PVAT. This data broadens our understanding of PVAT's physiological importance and suggests that PVAT can be a critical player in vascular homeostasis, emphasizing its regulatory role in mediating rosuvastatin-induced vasorelaxation through NO pathways. Further studies investigating the possible modulatory role of PVAT in the vasorelaxant effect of other statins would be promising.

Funding: *The author(s) received no financial support for the research.*

Conflicts of interest: *The authors declare that they have no conflict of interest.*

Ethics Committee Approval: *This study was approved by Ethics Committee of Istanbul University, Local Ethics Committee of Animal Experiments (Approval date:22/11/2023; Number:2267678)*

Peer-review: *Externally peer-reviewed.*

Author Contributions:

Research idea: DKD
Design of the study: DKD
Acquisition of data for the study: GRA, MA
Analysis of data for the study: DKD, GRA, MA
Interpretation of data for the study: DKD, BSUD,
Drafting the manuscript: DKD, BSUD, GRA, MA
Revising it critically for important intellectual content: DKD, BSUD,
Final approval of the version to be published: DKD, BSUD, GRA, MA

REFERENCES

[1] Lefer AM, Scalia R, Lefer DJ. Vascular effects of HMG CoA-reductase inhibitors (statins) unrelated to cholesterol lowering: New concepts for cardiovascular disease. Cardiovasc Res. 2001;49(2):281-287. DOI:10.1016/s0008-6363(00)00247-9

[2] Liao JK, Laufs U. Pleiotropic effects of statins. The Annual Review of Pharmacology and Toxicology 2004;45(1):89-118. DOI:10.1146/annurev.pharmtox.45.120.403.095748

[3] Zhou Q, Liao JK. Pleiotropic effects of statins – Basic research and clinical perspectives. Circulation Journal 2010;74(5):818-826. DOI:10.1253/circj.cj-10-0110

[4] Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circulation Research 2017;120(1):229-243. DOI:10.1161/circresaha.116.308537

[5] German CA, Liao JK. Understanding the molecular mechanisms of statin pleiotropic effects. Archives of Toxicology 2023;97(6):1529-1545. DOI:10.1007/s00204.023.03492-6

[6] Alvarez De Sotomayor M, Herrera MD, Marhuenda E, Andriantsitohaina R. Characterization of endothelial factors involved in the vasodilatory effect of simvastatin in aorta and small mesenteric artery of the rat. British Journal of Pharmacology 2000;131(6):1179-1187. DOI:10.1038/sj.bjp.0703668

[7] Bergdahl A, Persson E, Hellstrand P, Swärd K. Lovastatin induces relaxation and inhibits L-Type Ca^{2+} current in the rat basilar artery. Pharmacology & Toxicology 2003;93(3):128-134. DOI:10.1034/j.1600-0773.2003.930304.x

[8] Uydeş-Doğan BS, Topal G, Takır, S, İlkay F, Kaleli D, Özdemir O. Relaxant effects of pravastatin, atorvastatin and cerivastatin on isolated rat aortic rings. Life Sciences 2005;76(15):1771–1786. DOI:10.1016/j.lfs. 2004.11.002

[9] López J, Mendoza R, Cleva Villanueva G, Martínez G, Castillo EF, Castillo C. Participation of K^+ channels in the endothelium-dependent and endothelium-independent components of the relaxant effect of rosuvastatin in rat aortic rings. Journal of Cardiovascular Pharmacology and Therapeutics 2008;*13*(3), 207–213. DOI: 10.1177/107.424.8408321716

[10] López-Canales JS, Lozano-Cuenca J, López-Canales OA, Aguilar-Carrasco JC, Aranda-Zepeda L, López-Sánchez P, Castillo-Henkel EF, López-Mayorga RM, Valencia-Hernández I. Pharmacological characterization of mechanisms involved in the vasorelaxation produced by rosuvastatin in aortic rings from rats with a cafeteria-style diet. Clinical and Experimental Pharmacology and Physiology 2015;42(6):653-661. DOI:10.1111/1440-1681.12406

[11] Yildirim FIA, Kaleli Durman D, Aypar E, Ark M, Özdemir O, Doğan BSU. Atorvastatin acutely reduces the reactivity to spasmogens in rat aorta: implication of the inhibition of geranylgeranylation and MYPT-1 phosphorylation. Fundamental and Clinical Pharmacology 2015;30(2):96-106. DOI:10.1111/fcp.12173

[12] Ali N, Begum R, Faisal MS, Khan A, Nabi M, Shehzadi G, Ullah S, Ali W. Current statins show calcium channel blocking activity through voltage gated channels. BMC Pharmacology and Toxicology 2016;17(1). DOI:10.1186/s40360.016.0086-5

[13] Ali N, Ali W, Ullah A, Ahmad S, Hussain H, Ali W. Rosuvastatin and Simvastatin potentiate antihypertensive effect of amlodipine through vasorelaxation phenomenon. Pak J Pharm Sci. 2023;36(3):953-961.

[14] Kaleli-Durman D, Alp-Yıldırım Fİ, Özdemir O, Uydeş-Doğan BS. Relaxant effect of atorvastatin on isolated rat gastric fundus strips: implications for Ca^{2+}-signalling mechanisms. Canadian Journal of Physiology and Pharmacology 2019;97(5):413-421. DOI:1139/cjpp-2018-0723

[15] Nurullahoglu-Atalik K, Oz M, Shafiyi A. Rosuvastatin-induced responses in calf cardiac vein. Bratislavske Lekarske Listy 2015;116(8):494–498. DOI:10.4149/BLL_2015_095

[16] Nurullahoglu-Atalik KE, Yerlikaya H, Oz M, Esen H. Determining the Response to Statins in Rat Aorta Using High Fat Diet. Jordan Journal of Biological Sciences 2020;13(1):1-6.

[17] Şahintürk S. Rosuvastatin relaxes rat thoracic aorta, pulmonary artery, and trachea via nitric oxide, prostanoids, and potassium channels. Çukurova Medical Journal 2023;48(2):419-431. DOI:10.17826/cumj.1279122

[18] McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, Smith G, Warwick M. Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy – 3-methylglutaryl coenzyme A reductase inhibitor. The American Journal of Cardiology 2001;87(5):28-32. DOI:10.1016/s0002-9149(01)01454-0

[19] Cortese F, Gesualdo M, Cortese A, Carbonara, S, Devito F, Zito A, Ricci G, Scicchitano P Ciccone M. Rosuvastatin: Beyond the cholesterol-lowering effect. Pharmacol Res. 2016;107:1-18. DOI:10.1016/j.phrs.2016.02.012

[20] Mostaza JM, Escobar C. Rosuvastatin-Based Lipid-Lowering therapy for the control of LDL cholesterol in patients at high vascular risk. Journal of Clinical Medicine 2024;13(7):1894. DOI:10.3390/jcm13071894

[21] Nangle MR, Cotter MA, Cameron NE. Effects of rosuvastatin on nitric oxide–dependent function in aorta and corpus cavernosum of diabetic mice. Diabetes 2003;52(9):2396-2402. DOI:10.2337/diabetes.52.9.2396

[22] Sanna F, Margaritis M, Antoniades C. Perivascular adipose tissue as an endocrine organ: The role of statins. Current Pharmaceutical Design 2017;23(46):7055-7060. DOI:10.2174/138.161.2823666.170.926133843

[23] Zaborska KE, Wareing M, Austin C. Comparisons between perivascular adipose tissue and the endothelium in their modulation of vascular tone. British Journal of Pharmacology 2016;174(20):3388-3397. DOI:10.1111/bph.13648

[24] Balakumar P, Alqahtani A, Khan NA, Alqahtani T, Jagadeesh G. The physiologic and physiopathologic roles of perivascular adipose tissue and its interactions with blood vessels and the renin-angiotensin system. Pharmacological Research 2021;173:105890. DOI:10.1016/j.phrs.2021.105890

[25] Ahmed A, Bibi A, Valoti M, Fusi F. Perivascular adipose tissue and vascular smooth muscle tone: friends or foes? Cells 2023;12(8):1196. DOI:10.3390/cells12081196

[26] Wójcicka G, Jamroz-Wiśniewska A, Atanasova P, Chaldakov GN, Chylińska-Kula B, Bełtowski J. Differential effects of statins on endogenous H2S formation in perivascular adipose tissue. Pharmacological Research 2010;63(1):68-76. DOI:10.1016/j.phrs.2010.10.011

[27] Percie Du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen O, Rawle F, Peynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Wurbel H. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biology 2020;18(7):e3000410. DOI:10.1371/journal.pbio.3000410

[28] Blanco-Rivero J, De Las Heras N, Martín-Fernández B, Cachofeiro V, Lahera V, Balfagón G. Rosuvastatin restored adrenergic and nitrergic function in mesenteric arteries from obese rats. British Journal of Pharmacology 2010;162(1):271-285. DOI:10.1111/j.1476-5381.2010.01030.x

[29] Zhao Y, Vanhoutte PM, Leung SWS. Vascular nitric oxide: Beyond eNOS. Journal of Pharmacological Sciences 2015;129(2):83-94. DOI:10.1016/j.jphs.2015.09.002

[30] Barp CG, Bonaventura D, Assreuy J. NO, ROS, RAS, and PVAT: More Than a Soup of Letters. Frontiers in Physiology 2021;12,640021. DOI:10.3389/fphys.2021.64002

How to cite this article: Kaleli Durman D, Aktaş GR, Aras M, Uydeş Doğan BS . Relaxant Effect of Rosuvastatin in Isolated Rat Aorta with Perivascular Adipose Tissue. Clin Exp Health Sci 2024; 14: 1127-1132. DOI: 10.33808/clinexphealthsci.1561664