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Konstantinos Toutouzas, MD, PhD, Antonios Karanasos, MD, PhD, Dimitris Tousoulis, MD, PhD

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Exercise versus targeting of endocannabinoid system for atheromatic plaque stabilization. Opposing or complementary roles?

Konstantinos Toutouzas, MD, PhD, Antonios Karanasos, MD, PhD, Dimitris Tousoulis, MD, PhD

1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

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Corresponding author:
Konstantinos Toutouzas
Hippokration Hospital,
114, Vas.Sofias Av
11528, Athens, Greece
Tel: 30-2132088026
E-mail: ktoutouz@gmail.com

Exercise is a cornerstone in improving cardiovascular outcomes not only in patients with established cardiovascular disease, but also in patients with conditions posing a high risk for future cardiovascular events.[1, 2] Numerous hypotheses have been suggested over the potential pathways which mediate the positive effects of exercise on the cardiovascular system, with the majority of the mechanisms involving effects on the reduction of cardiovascular risk factors, while a direct protective effect on atherosclerotic plaque has been suggested. [3]

The endocannabinoid system (CB) has been implicated in the pathogenesis of cardiovascular disease, through complex interactions including among others effects on the immune system, effects on endothelium, and involvement in the lipid metabolism.[4] Consequently, approaches to target the CB system have been used in order to improve cardiovascular outcomes.[5] In the STRADIVARIUS trial rimonabant, a CB1 receptor blocker, was shown to reduce plaque burden compared to placebo,[6] however the drug was soon withdrawn from the market following randomized studies showing a lack of benefit and increased psychiatric side-effects.[7]

Katsimpoulas et al[8] in the current issue of the journal are investigating whether exercise, inhibition of the endocannabinoid system, or their combination can exert a plaque stabilizing effect on an experimental mouse model of atherosclerosis. They used apolipoprotein E-deficient (ApoE-/-) mice kept on a 16-week high-fat diet which they divided in 4 groups: a control group, a group receiving rimonabant, a CB1 receptor blocker, a group subjected to exercise training on treadmill and a group allocated to both rimonabant and exercise training. Not surprisingly and in line with previous reports from the same group[9], exercise was associated with a lower plaque area, a higher relative concentration of collagen and elastin, and a reduced plaque

content of macrophages compared to the control group. Similarly, within-plaque TIMP-1 concentration was increased in the exercise group compared to control as were both the serum and within-plaque concentrations of MMP-3 and MMP-9. The observed effects with exercise were identical in the rimonabant group versus control, and also in the group with the combination of rimonabant with exercise training. Interestingly, the combined treatment group failed to show superiority over each of the treatments alone, with the exception of plaque macrophage content that was lower with the combined treatment compared to either exercise or rimonabant alone.

These findings collectively suggest that rimonabant treatment can exert favorable actions on atherosclerosis which is comparable to the effect of exercise, and could thus potentially stabilize atheromatic plaques to a similar extent. This could be of particular benefit in metabolic syndrome, a condition that has been associated with impaired function of the CB system, and has also been shown to be associated with a vulnerable plaque phenotype.[10] However, the finding of an absence of a synergistic action of these two treatments suggests that common pathways are implicated in the plaque stabilizing effects that these two treatments exert. Indeed, the CB1 system has been shown to be regulated from exercise, with medium- to high-intensity voluntary exercise demonstrating an increase in CB signaling, via increased serum anandamide levels and possibly increased CB1 expression[5]. As also demonstrated in the current study, both interventions induced similar decrease in serum and within-plaque matrix metalloproteinases (MMPs), enzymes that have been associated with plaque instability. This plaque stabilizing effect has been shown after administration of statins, with imaging evidence of a reduction in plaque volume and a thickening of the fibrous cap in fibroatheromas which was observed in conjunction with a decrease in levels of circulating MMPs.[11, 12] Whether this cap thickening observed in in vivo

human studies would parallel the structural molecular changes in elastin and collagen is unknown, as modalities able to assess such information in vivo have only just recently been applied in human subjects.[13] Overall, the current study demonstrates a similar effect of exercise and CB system inhibition in atheromatic plaque stabilization, possibly through a similar pathway involving MMP suppression.

Thus, translation of the findings of the current study to a possible clinical role for CB inhibition in plaque stabilization should be done with extreme caution, given these similar mechanisms of action of rimonabant and exercise implied by the present study. It could be speculated that more selective CB inhibitory drugs, devoid of the psychiatric side-effects of rimonabant, could be used for plaque stabilization in clinical subjects. Although such a favorable effect from selective CB inhibition could indeed also be observed in human subjects, in line with plaque regression demonstrated with rimonabant in human,[6] it is doubtful what the additive clinical value of such an approach would be, over the current recommendation of regular exercise already incorporated in current guidelines[1]. Therefore, the most important lesson to extract from this experimental study is to try and reinforce prevention strategies on a population level that focus on promoting physical exercise on people at increased risk for cardiovascular events, as exercise can effectively stabilize plaques at the same extent as inhibition of the CB system, being free of the side-effects of CB1 inhibition.

References.

[1] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European journal of preventive cardiology. 2016;23:NP1-NP96.

[2] Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European heart journal. 2013;34:3035-87.

[3] Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events. Journal of the American College of Cardiology. 2016;67:316-29.

[4] Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. Clinical cardiology. 2012;35:329-35.

[5] McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PloS one. 2014;9:e89566.

[6] Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, Cannon CP, Deanfield JE, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. Jama. 2008;299:1547-60.

[7] Topol EJ, Bousser MG, Fox KA, Creager MA, Despres JP, Easton JD, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet. 2010;376:517-23.

[8] Katsimpoulas M, Kadoglou NE, Moustardas P, Kapelouzou A, Dede E, Kostomitsopoulos N, et al. The role of exercise training and endocannabinoid system in atherosclerotic plaque burden and composition in Apo-E deficient mice. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese.

[9] Kadoglou NP, Kostomitsopoulos N, Kapelouzou A, Moustardas P, Katsimpoulas M, Giagini A, et al. Effects of exercise training on the severity and composition of atherosclerotic plaque in apoE-deficient mice. Journal of vascular research. 2011;48:347-56.

[10] Synetos A, Papanikolaou A, Toutouzas K, Georgiopoulos G, Karanasos A, Drakopoulou M, et al. Metabolic syndrome predicts plaque rupture in patients with acute myocardial infarction. An optical coherence study. International journal of cardiology. 2016;209:139-41.

[11] Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. Journal of the American College of Cardiology. 2014;64:2207-17.

[12] Ogita M, Miyauchi K, Morimoto T, Daida H, Kimura T, Hiro T, et al. Association between circulating matrix metalloproteinase levels and coronary plaque regression after acute coronary syndrome--subanalysis of the JAPAN-ACS study. Atherosclerosis. 2013;226:275-80.

[13] van der Sijde JN, Karanasos A, Villiger M, Bouma BE, Regar E. First-in-man assessment of plaque rupture by polarization-sensitive optical frequency domain imaging in vivo. European heart journal. 2016;37:1932.