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## EDITORIAL

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



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.<sup>1,2</sup> 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.<sup>3</sup>

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.<sup>4</sup> Consequently, approaches to target the CB system have been used in order to improve cardiovascular outcomes.<sup>5</sup> In the STRADIVARIUS trial rimonabant, a CB1 receptor blocker, was shown to reduce plaque burden compared to placebo,<sup>6</sup> however the drug was soon withdrawn from the market following randomized studies showing a lack of benefit and increased psychiatric side-effects.<sup>7</sup>

Katsimpoulas et al<sup>8</sup> 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<sup>-/-</sup>) 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,<sup>9</sup> 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.<sup>10</sup> 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.<sup>5</sup> 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

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circulating MMPs.<sup>11,12</sup> 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.<sup>13</sup> 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,<sup>6</sup> 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.<sup>1</sup> 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.

## Conflict of interest

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