The Polyunsaturated Fatty Acids EPA and DHA Prevent Myocardial Infarction-induced Heart Failure by Inhibiting p300-HAT Activity in Rats

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Introduction: While the cardioprotective functions of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and omega-3 unsaturated fatty acids have been previously demonstrated, little is known about their effects on cardiomyocyte hypertrophy. In this study, we compared the effects of EPA and DHA on hypertrophic responses in cardiomyocytes and development of heart failure in rats with MI.

Methods and results: Both EPA and DHA significantly suppressed phenylephrine- and p300-induced cardiomyocyte hypertrophy, transcription of hypertrophy response genes, and acetylation of histone H3K9 in cardiomyocytes. EPA and DHA directly inhibited p300-histone acetyltransferase activity (IC50: 37.8 and 30.6 µM, respectively). Further, EPA and DHA induced allosteric inhibition of histones and competitive inhibition of acetyl-CoA, and significantly prevented p300-induced hypertrophic responses. Rats with moderate MI (left ventricular fractional shortening [FS] <40%) were randomly assigned to three groups, namely, vehicle (saline), EPA (1 g/kg), and DHA (1 g/kg). One week after the operation, rats were orally administrated with test agents for 6 weeks.

Echocardiographic analysis demonstrated that both EPA and DHA treatments preserved FS and prevented MI-induced left ventricular remodelling. Furthermore, EPA and DHA significantly suppressed the MI-induced increase in myocardial cell diameter, perivascular fibrosis, mRNA levels of hypertrophic markers, fibrosis, and acetylation of histone H3K9. The effects on hypertrophic responses and the development of heart failure were not different between EPA and DHA groups.

Conclusion: Both EPA and DHA suppressed hypertrophic responses and the development of heart failure to the same extent through the inhibition of p300-HAT activity. ❑