Cytochrome P450 epoxygenase activity contributes to n-3 polyunsaturated fatty acids-induced BK channels activation in diabetic rats

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Introduction: n-3 polyunsaturated fatty acids (n-3 PUFAs), which mainly include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are known to protect the coronary large conductance Ca\textsuperscript{2+}-activated K\textsuperscript{+} (BK) channel function in diabetic rats. However, the mechanisms remain unclear. The objective of this study was to examine the regulation role of cytochrome P450 epoxygenase in n-3 PUFAs-induced BK channels activation in diabetic rats.

Methods: The effects DHA and EPA on coronary artery tension were measured using a myograph system. BK channel currents were determined by the patch clamp technique. The mRNA and protein expressions of BK channel subunits were measured using qRT-PCR and western blots. The Ca\textsuperscript{2+} concentrations of the coronary smooth muscle cells were measured using and fluorescence Ca\textsuperscript{2+} indicator.

Result: Both DHA and EPA relaxed coronary arterial rings pre-constricted by endothelin-1 in control and diabetic rats, which was significantly inhibited by preincubation with a specific BK channel blocker iberiotoxin. Consistent with DHA, EPA activated BK channels currents in a concentration dependent manner in fresh isolated coronary smooth muscle cells. The activation effects were inhibited by preincubation with a cytochrome P450 epoxygenase inhibitor, SKF525A. Oral administration of n-3 PUFAs enhanced BK-β1 expression without altering BK-α levels, activated BK channels currents, decreased cytosolic Ca\textsuperscript{2+} concentrations in coronary smooth muscle cells and protect coronary vasoreactivity in both control and diabetic rats; however, all these effects were significant weaken in diabetic rats in addition to SKF525A intraperitoneal injection.

Conclusion: These results suggest that n-3 PUFAs-mediated coronary vasodilatation is mediated by activation of BK channels through cytochrome P450 epoxygenase in diabetic rats.