**ABSTRACT**

Cardiovascular diseases, particularly acute myocardial infarction, are one of the leading causes of death in developed countries. It is well known that adaptation to chronic intermittent hypobaric hypoxia (IHH) confers long-lasting cardiac protection against acute ischemia/reperfusion injury. Protein kinase C (PKC) appears to play a role in its cardioprotective mechanism since the administration of general PKC inhibitor completely abolished the improvement of ischemic tolerance in IHH hearts. However, the involvement of individual PKC isoforms remains unclear. Therefore, the primary aim of this study was to investigate the potential involvement of PKCδ and PKCε, the most prevalent PKC isoforms in rat heart, in the mechanism of IHH-induced cardioprotection. We showed that IHH up-regulated PKCδ protein in left ventricle, enhanced its phosphorylation on Ser643 and increased its co-localization with markers of mitochondrial and sarcolemmal membranes. PKCδ subcellular redistribution induced by IHH as well as the infarct size-limiting effect of IHH was reversed by acute treatment with PKCδ inhibitor rottlerin. These data support the view that PKCδ plays a significant role in IHH-induced cardioprotection. On the other hand, adaptation to IHH decreased the PKCε total protein level without affecting its subcellular distribution and the level of phosphorylated PKCε (Ser729). Moreover, we demonstrated that the PKCε inhibitor peptide KP-1633 was not able to block the protective effects of IHH in isolated left ventricular myocytes exposed to metabolic inhibition/reenergization, simulating acute ischemia/reperfusion injury. These findings support the idea that PKCε is not a key player in cardioprotection induced by IHH.

Furthermore, we assumed that the increased accumulation of n-3 polyunsaturated fatty acids (n-3 PUFAs) in myocardial phospholipids induced by IHH may contribute to improved ischemic tolerance. PKC activity and function are influenced by lipid membrane composition and by the quality of lipid signaling molecules such as diacylglycerols (DAGs). The second goal of this study was to find out whether an altered phospholipid FA profile by diets enriched with saturated FAs (SFAs), n-3 PUFAs and n-6 PUFAs, plays a role in the cardioprotective mechanism of IHH in a PKC-dependent manner. Whereas the (SFA+monounsaturated FA)/PUFA ratio in heart DAGs corresponded to the ratio in the respective diet (in the sequence SFA>n-3 PUFA>n-6 PUFA diet), heart phospholipids maintained constant content of SFAs, monounsaturated FAs and total PUFAs, independent of diet and IHH. On the other hand, the n-6/n-3 PUFA ratio was influenced to various extents by either the dietary PUFA supply or IHH in both heart phospholipids and DAGs. Whereas the groups fed on SFA and n-3 PUFA enriched diets were protected by IHH, the protective effect of the n-6 PUFA-enriched diet on myocardial infarct size was not further enhanced by adaptation to IHH. As the IHH-induced decrease in n-6/n-3 PUFA ratio in membranes was proportional in all groups, it seems unlikely that this response is directly involved in the mechanism of infarct size-limiting effect in IHH hearts. The infarct size decreased with increasing relative PKCε protein content within the normoxic or hypoxic groups, which is in line with a generally accepted view that this PKC isoform is cardioprotective. However, all hypoxic groups had smaller infarction and lower PKCε content, suggesting that IHH protects the myocardium by a mechanism independent of PKCε. Unlike in other diet groups, IHH did not increase myocardial ischemic tolerance and did not cause up-regulation of PKCδ protein in rats supplemented with n-6 PUFA-enriched diet. The relative content of PKCδ in myocardial particulate fraction exhibited a close negative correlation with myocardial infarct size. These results suggest that PKCδ plays an important role in the infarct size-limiting mechanism of IHH in adult rat hearts.