α1A-adrenergic receptors activate phospholipase C, but suppress Ins(1,4,5)P3 generation during ischemia-reperfusion in mouse heart

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Reperfusion of ischemic rat or mouse hearts causes noradrenaline (Nor) release, stimulation of α1-adrenergic receptors (α1-AR), phospholipase C (PLC) activation, Ins(1,4,5)P3 generation and consequent arrhythmias. We examined the effect of heightened activity of α1A-AR on these responses. [3H]Inositol-labeled mouse hearts overexpressing α1A-AR (α1A-TG) showed 10 fold higher PLC responses to Nor than wild type controls (α1A-WT). Isolated, perfused α1A-TG and α1A-WT hearts were subjected to 20 or 30 min zero-flow ischemia followed by 2 min reperfusion and [3H]-labeled inositol phosphates were extracted and quantified. Reperfusion of α1A-WT hearts after 30 min ischemia caused substantial [3H]Ins(1,4,5)P3 generation, from 1011 ± 99 to 2274 ± 297 cpm/heart, mean ± SEM, n=6 $p<0.01$. There was no detectable increase in [3H]Ins(1,4,5)P3 when α1A-WT hearts were reperfused after 20 min ischemia. However, reperfusion after 20 min ischemia with 100 μM Nor added to the perfusate caused generation of [3H]Ins(1,4,5)P3 in α1A-WT, from 662 ± 121 to 2554 ± 773, $p < 0.01$. In marked contrast to α1A -WT, [3H]Ins(1,4,5)P3 was not generated in α1A-TG hearts after either 20 or 30 min ischemia, even when Nor was added. Despite this, the overall reperfusion-induced PLC response (measured by increases in total [3H]InsPs) was 3-5 fold higher in α1A-TG than in α1A-WT after either 20 or 30 min ischemia. Both α1A-WT and α1A-TG showed substantially heightened responses to added Nor during 2 min reperfusion compared with normoxic conditions, 10 fold for α1A-WT and 2-3 fold for α1A-TG. These findings show that heightened activity of α1A-AR protect the myocardium from large increases in Ins(1,4,5)P3 by a mechanism that does not involve inhibition of PLC.