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Title: Sulfhydryl oxidation of myofibrillar proteins and its effect on the contractile function in human cardiomyocytes

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Summary

The role of oxidative stress and sulfhydryl (SH) oxidation is well established in ischaemic reperfusion injury and heart failure, although the mechanism of the development of the mechanical depression is not clear. In this study we aimed to investigate the SH oxidation of myofibrillar proteins and its influence on the Ca^{2+}-activated contractile force (F_o), the Ca^{2+}-independent passive force ($F_{passive}$), and the kinetics of actin myosin cycle (force generation) (k_{tr}). SH oxidation was investigated by 2,2'-dithiodipyridine (DTDP) and peroxinitrite, and the reversion was studied by dithiotreitol (DTT), reduced glutation (GSH) and N-acetyl-L-cysteine, *in vitro*.

DTDP evoked a decrease in F_o in paralel with the oxidation of SH groups of contractile proteins (EC_{50}=2.46±0.22 mM). The mechanical and biochemical alterations were further investigated upon 2.5 mM DTDP treatments. F_o decreased to 64% at this intermediate DTDP concentration, similarly to the Ca^{2+}-sensitivity (ΔpCa_{50}=0,22±0,02), and the k_{tr} (to 75 %), while $F_{passive}$ was slightly elevated (10% increase). These mechanical alterations were accompanied by decrease in SH content to 15%. DTT fully reverted all the mechanical alterations exept the $F_{passive}$, while GSH and NAC were able to induce only partial reversion in the SH content and even worsened the contractile parameters. In addition, myosin light chain 1 and actin were identified as contractile proteins which may mediate these mechanical alterations.

The possible role of SH oxidation in the peroxinitrite induced contractile depression was also investigated. 50 µM peroxinitrite decreased the F_o to 56±4% which was partially reverted by 10 mM DTT and 10 mM NAC to 69 ± 4% and 71 ± 7%, respectively. This suggests that SH oxidative effect of peroxinitrite contributes to the reduction in the Ca^{2+}-activated contractile force in a reversible manner.

These data suggests that the Ca^{2+}-activated contractile force (F_o), the Ca^{2+}-independent passive force ($F_{passive}$), and the kinetics of actin myosin cycle is in close relationship with the SH status of the myofibrillar proteins. SH oxidation of myofibrillar proteins may contribute to the contractile dysfunction in ischaemic reperfusion injury and heart failure. The reversibility of these effects emphasize the therarpeutic potential of the properly applied antioxidant treatment.

Key words: ischaemia, sulfhydryl, contractile function, oxidative stress

Kulcsszavak: ischaemia, szulfhidril, kontraktilis funkció, oxidatív stressz