Effects of hydrogen peroxide on vascular tone in isolated rat mesenteric artery

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1. The effects of hydrogen peroxide (H_2O_2) on basal tone, 5 HT-and high K-induced contractions were investigated in ring preparations isolated from rat mesenteric artery. Changes in cytosolic Ca^{2+} concentration and cellular ATP contents in response to H_2O_2 were also examined.

2. H_2O_2 induced slow developing and sustained contractions in a concentration-dependent manner, regardless of the presence or absence of endothelium. The contractile response to H_2O_2 at higher (3 mM) but not at lower (1 mM) concentrations was reduced by the removal of endothelium.

3. H_2O_2-induced contractions were not inhibited by nifedipine, the removal of extracellular Ca^{2+} and thapsigargin under extracellular Ca^{2+}-free condition. FCCP (uncoupler of oxidative phosphorylation in mitochondoria) shortened the time-to-peak of contraction induced by H_2O_2. Both PKC and MAPK inhibitors failed to inhibit H_2O_2 -induced contractions.

4. H_2O_2 increased intracelullar Ca^{2+} concentration both in the presence and absence of extracellular Ca^{2+}. H_2O_2 did not affect Ca^{2+}-induced contraction in skinned arterial preparations.

5. H_2O_2 significantly reduced cellular ATP contens in the rat thoracic aorta.

6. Contractions evoked by 5 HT or KCl were potentiated by H_2O_2 at low concentrations but inhibited at high concentrations. The inhibitory effect of H_2O_2 was reversible and endothelium-independent.

7. These results suggest that H_2O_2 caused extracellular Ca^{2+}-and endothelium-independent, sustained contractions accompanied with sustained rise in Ca^{2+} concentration. The H_2O_2-induced contractions seem to be partly related to mitochondrial dysfunction, but not Ca^{2+} release from the endoplasmic reticulum, activations of PKC and MAPK and change in Ca^{2+} sensitivity to contractile machinery. These vasoactive responses to H_2O_2 may explain some causes of abnormal vasoreactivity due to oxidative stress, produced by inflammation, ischemic-reperfusion injury and atherosclerosis.