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CARDIOPROTECTIVE EFFECTS OF N-ACETYLCYSTEINE (NAC) AND ISOSORBIDE-5-MONONITRATE (IS5MN) AFTER ISCHEMIA AND REPERFUSION IN A RAT MODEL

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NAC is a thiol-containing agent which replenishes glutathione stores. NAC also acts as a free radical scavenger specific to H_2O_2 and $OH^{\bullet}$ and may thereby limit reperfusion injury after ischemia. NAC can potentiate the clinical efficacy of a nitrate donor in unstable angina. However the evidences on cardioprotection by NAC and on its mechanism of action are still controversial. Here, we evaluated the efficacy of NAC and isosorbide 5-mononitrate (IS5MN) in cardiac ischemia and reperfusion.

Methods. Cardiac ischemia was performed by ligation of the left coronary artery for 30 min followed by 24 hours (early) or 7 days (late) of reperfusion in adult rats. NAC (200 mg/kg BW) was infused from 5 min before to the end of reperfusion. IS5MN (200 mg/kg BW) was given by gavage b.i.d. At 24 hours, area-at risk (AAR, Evans blue) and necrotic area (tetrazolium chloride) were measured histologically in LV myocardium of rats treated with either NAC (n= 8), IS5MN (n= 8), their combination (n= 10) or a vehicle (n= 18). Infiltrating leukocytes (naphtol-AS-D chloroacetate esterase) were counted in 5 µm histological sections from vehicle and combination groups. At 7 days, hemodynamic measurements were performed on anaesthetised animals treated with vehicle (n= 16) or NAC+IS5MN (n= 9).

Results. AAR were comparable among all groups (range 37-43 % LV area). After 24 hours of reperfusion, NAC+IS5MN reduced MI size (29±6 % AAR) compared to the vehicle group (59±4 %), but not NAC (49±8 %) or IS5MN (41±5 %) alone. NAC+IS5MN also attenuated leukocyte infiltration in AAR (226±36 vs 315±43/mm^2, p= 0.002). At 7 days of reperfusion, the combination therapy did not modify infarct size vs vehicle (16±3 vs 18±1 % AAR, p= 0.55), but significantly reduced LVEDP (5±1 vs 9±1 mmHg, p= 0.01) and diastolic wall stress (62±7 vs 123±18 dynes/mm^2, p= 0.02).

Conclusions. When given at reperfusion, the association of NAC and IS5MN significantly reduced acute cardiac damage (infarct area and inflammation) whereas either agent seemed ineffective. The acute cardioprotective benefits of the association are maintained after 1 week of reperfusion, as reflected by a reduction of diastolic wall stress, a strong determinant of LV remodelling.