Role of the mevalonate pathway in myocardial postconditioning

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We have previously reported that chronic oral treatment with the HMG-CoA reductase inhibitor lovastatin shows cardioprotection but interacts with the cardioprotective effect of postconditioning and that farnesol, a key intermediate of the mevalonate pathway, is cardioprotective possibly via enhancement of protein geranylgeranylation. Here we studied the interaction of the HMG-CoA reductase inhibitor atorvastatin and farnesol with postconditioning.

Male Wistar rats were orally treated with vehicle (2.5% methylcellulose), 10 mg/kg/day atorvastatin, 1 mg/kg/day farnesol, or their combination, respectively, for 12 days. At the end of the treatments, hearts were isolated and perfused according to Langendorff. Hearts were subjected to 30 minutes of coronary occlusion and 120 minutes of reperfusion with or without a postconditioning protocol induced by six intermittent periods of ischemia/reperfusion of 10-s duration each. At the end of the perfusion protocol, infarct size was determined by standard triphenyltetrazolium chloride staining and expressed as % of the area at risk.

We found that postconditioning significantly decreased infarct size (19.5 ± 4.1% vs. 40.0 ± 2.9%, p < 0.05). Atorvastatin pretreatment significantly decreased infarct size (17.7 ± 2.9%, p < 0.05), however, atorvastatin inhibited the cardioprotective effect of postconditioning (40.4 ± 2.9%). Farnesol alone significantly decreased infarct size (22.3 ± 3.9%, p < 0.05), however, it also inhibited cardioprotection by postconditioning (41.5 ± 6.9%). The combination of atorvastatin and farnesol did not show protection (39.3 ± 6.3%), however, their combination with postconditioning was again protective (19.9 ± 3.7%, p < 0.05).

These results show that the mevalonate pathway plays a complex role in ischemia/reperfusion injury and cardioprotection by postconditioning, however, the cellular mechanism of the observed effects of atorvastatin and farnesol needs further investigation.