[gw22-e0940]

RESVERATROL ATTENUATES MYOCARDIAL ISCHEMIA/REPERFUSION INJURY VIA UPREGULATING ADIPONECTIN LEVEL AND MULTIMERISATION IN TYPE 2 DIABETIC MICE

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10.1136/heartjnl-2011-300867.85

Objectives type 2 diabetes (T2DM) exacerbated myocardial ischemia/reperfusion (MI/R) injury, accompanied by significantly lower adiponectin (APN) level and diminished APN multimerisation. Resveratrol, a natural polyphenol, promotes APN up-regulation and multimerisation both in adipocytes and mice by up-regulation of DsbA-L (a recently identified protein that facilitates APN multimerisation and stability). Therefore, the present study aimed to observe whether RSV attenuates MI/R injury in T2DM, and if so, to further investigate the underlying mechanisms.

Methods T2DM was induced by high-fat diet (HD) feeding plus low-dose streptozotocin (STZ) injection. Mice received an HD since three weeks old for eight weeks. After three weeks of HD feeding, mice were intraperitoneally injected with 100 mg/kg STZ (Sigma). T2DM was confirmed by markedly elevated fasting-blood glucose level (>11.1 mmol/l) five weeks after injection. Mice were treated with 10 mg/kg RSV daily by intragastric administration for three weeks since five weeks of HD feeding. Compound C (an AMPK inhibitor) was administrated by intraperitoneal injection with 20 ug/g one h before MI/R. Mice were subjected to 30 min of ischemia and three h or 24 h of reperfusion.

Results HD feeding plus low-dose STZ injection successfully induced T2DM. Compared to normal control, diabetic mice manifested higher fasting-blood glucose level, lower glucose tolerance in OGTT examination (n=12, $p<0.05$), but there

was no difference in plasma insulin levels. RSV alleviated MI/R injury in both normal and diabetic mice, as evidenced by decreased infarct size, cardiomyocytes apoptosis, caspase-3 activity, improved cardiac function (n=10, all $p<0.05$). Moreover, RSV treatment improved APN level, upregulated APN multimerisation both in plasma and adipose tissue, and increased DsbA-L expression in adipose tissue in diabetic mice (all $p<0.01$). Conversely, administration of AMPK inhibitor Compound C significantly attenuated the cardioprotective effects of RSV (all $p<0.05$).

Conclusions RSV upregulates adiponectin level and multimerisation in both plasma and adipose tissue in T2DM, and therefore attenuates MI/R injury.