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Leptin Involved in Cardioprotection Induced by Spontaneous Caloric Restriction

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Background:

Experimentally imposed caloric restriction (CR) leads to increased resistance to cardiac ischemic injury in a manner dependent on circulating adiponectin and activated AMPK, both increasing under CR. Transgenic αMUPA mice spontaneously consume less food (~20%) compared to their wild type (WT) control mice and resemble CR animals in showing improved health and increased life span.

Objective:

Here we investigated for the first time if and how αMUPA mice exhibit cardioprotection when fed *ad libitum*at young and old ages.

Methods and Results:

Under left anterior descending (LAD) coronary artery ligation *in vivo*, the oldest WT mice (24 months) all died within the first ischemic day, whereas 50 % αMUPA mice survived after 7 days still showing 41% fractional shortening (FS). At younger ages, αMUPA mice showed improved FS and decreased left ventricular dilatation and inflammation compared to WT mice ($p<0.05$). Similarly, reduced functional and histological damage was detected in young αMUPA mice after 24h LAD ligation or in the Langendorff ischemia/reperfusion model. At baseline, αMUPA and WT mice did not differ in the serum levels of adiponectin, but αMUPA showed 60% increased leptin, an adipokine that regulates satiety and metabolism and decreases under CR. In the cardiac tissue at baseline, αMUPA mice did not show changes in activated AMPK, however exhibited significantly increased levels of activated AKT and total SIRT1, a cellular nutritional sensor. The improvement in cardiac functional and histological parameters, as detected after 24h LAD ligation, were abrogated by pretreating αMUPA mice with antibodies against leptin or with AG490 or Wortmannin that inhibit leptin signaling. Importantly, all three agents did not affect the WT mice.

Conclusion:

The αMUPA phenotype attenuates cardiac aging and confers an intrinsic metabolic state of preconditioning, different from that of CR. It leads to cardioprotectin through the pathway of leptin/JAK2/PI3K/AKT and probably involves SIRT1.