Imposed Vs. Spontaneous Caloric Restriction Reduces Cardiac Ischemic Injury through Distinct Pathways

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Imposed caloric restriction (CR) extends longevity in mammals and attenuates age-related diseases including ischemia-induced cardiac injury. Adiponectin, an adipokine that increases under starvation and senses the cellular energy status, has been implicated in CR-induced cardioprotection. Transgenic αMUPA mice fed ad libitum spontaneously consume less food (~25%) compared to wild-type (WT) control mice (FVB/N). αMUPA mice share many similarities with CR animals including improved health and increased life span. Here we investigated the response of αMUPA mice to ischemic stress in vivo compared to control mice both under ad libitum feeding. We also studied the response of C57Bl mice fed 65% of their spontaneous food consumption for two weeks compared to ad libitum fed C57Bl mice. Mice were tested after ligation of left anterior descending (LAD) coronary artery for 24 hours. Both αMUPA and CR C57Bl mice showed better contractile functions, weaker inflammatory responses and smaller infarct sizes ($p<0.05$). CR C57Bl, but not αMUPA mice, also demonstrated significantly reduced numbers of apoptotic cells. Moreover, CR C57Bl mice showed increased adiponectin levels (~45%) in the serum and reduced levels of leptin (~60%), an adipokine associated with satiety and energy status. Conversely, αMUPA exhibited increased levels of leptin (60%) with no changes in adiponectin. Furthermore, the aforementioned improvement in cardiac parameters after LAD ligation was abrogated by treating αMUPA mice with antibodies for leptin, or with AG490 and Wartmannin that interfere with leptin signaling. In addition, both