Fitness Impacts Susceptibility for Obesity and Metabolic Disease

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Aerobic capacity/fitness significantly impacts mortality and susceptibility for metabolic diseases such as fatty liver and diabetes, but the mechanisms remain unknown. We utilize rats selectively bred for high (HCR) and low (LCR) intrinsic aerobic capacity to examine the mechanisms by which aerobic capacity impacts metabolic vulnerability for fatty liver, insulin resistance, and obesity following acute and chronic high fat diets. Our studies have shown that there are key differences in regulation of energy balance, substrate utilization and trafficking, and hepatic mitochondrial function between strains that all likely play a role in the low fit LCR rats being more susceptible to metabolic dysfunction. Hepatic gene arrays following acute high fat diets have also revealed that the bile acid synthesis pathway is up-regulated in the high fit-HCR rats suggesting that this may be a mechanisms for elevated energy expenditure and/or fecal elimination of excess energy. Low fit-LCR rats also display a collapse of hepatic fatty acid oxidation and mitochondrial function that tracks with dramatic increases in liver triglycerides following chronic high fat diets, while the HCR rats maintain mitochondrial function and are protected against the development of steatosis. In addition, chronic high fat diets with 1% cholesterol, which is commonly used to evoke a non-alcoholic steatohepatitis, show that the LCR develop significant hepatic-inflammation, -necrosis, and –apoptosis, while the high fit HCR animals appear relatively protected despite hepatomegaly occurring in both groups. Finally, recent data suggests that hepatic energy state, modulated by fatty acid oxidation, impacts energy intake through as of yet unknown mechanisms. In conclusion, these studies are beginning to reveal mechanisms by which fitness, through hepatic differences in metabolism, impact susceptibility for obesity and metabolic disease.