Chronic mild stress improves glucose homeostasis via myonectin-mediated suppression of sympathetic activity in high-fat diet-fed mice

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Objective Recent studies suggest that chronic stress exposure can ameliorate the progression of diet-induced prediabetic disease, by inhibiting an increase in weight gain, caloric intake and efficiency and insulin resistance. To determine the underlying mechanism by which chronic stress improves the progression of type 2 diabetes, we developed a model of chronic mild stress in high-fat diet (HFD)-fed mice which are resistant to obesity and exhibit a healthy-like metabolic phenotype.

Methods High-fat diet (HFD): 45% kcal derived from fat (Research Diets, Inc.). Mice experienced one stressor during the day and a different stressor during the night. Stressors were randomly chosen from the following list: cage tilt on a 45° angle for 1 to 16 h; food deprivation for 12 to 16 h; white noise for 1 to 16 h; strobe light illumination for 1 to 16 h; crowded housing; light cycle (continuous illumination) for 24 to 36 h; dark cycle (continuous darkness) for 24 to 36 h; water deprivation for 12 to 16 h; damp bedding (200 ml water poured into sawdust bedding) for 12 to 16 h. Recombinant adeno-associated virus (AAV): AAV9 vectors encoding myonectin under the control of the ubiquitous CMV promoter (AAV9-CMV-Vip) or an equal dose of the AAV9-CMV-null vector were delivered to C57BL/6 mice by the tail vein. Mice were deprived of food for 16 h and then subjected to test 7 days after AAV injection.

Results Chronic stress improved glucose intolerance and sympathetic overactivity in HFD-fed mice. Chronic stress attenuated epinephrine (EPI)-stimulated glycerol release into blood in vivo and accelerated glycerol release from white adipose tissue followed by in vitro incubation with EPI. Chronic stress reduced plasma triglyceride but increased the levels of plasma insulin and myonectin. We further found that adeno-associated virus 9 (AAV9)-mediated myonectin overexpression improved glucose homeostasis and reduced epinephrine sensitivity. Myonectin overexpression reduced plasma norepinephrine, EPI and leptin levels, and increased insulin sensitivity in brown and white adipose tissue. Intense sympathetic activity with high-intensity running inhibited myonectin expression in skeletal muscle, whereas medium and low-intensity exercise running increased myonectin expression.

Conclusions These findings suggest that chronic mild stress can improve glucose homeostasis via myonectin-mediated suppression of sympathetic activity in high-fat diet-fed mice.