
Abstract
Mitochondrial dysfunction is both a contributing mechanism and complication of diabetes, and oxidative stress contributes to that dysfunction. Mitochondrial manganese-superoxide dismutase (MnSOD) is a metalloenzyme that provides antioxidant protection. We have previously shown in a mouse model of hereditary iron overload that cytosolic iron levels affected mitochondrial manganese availability, MnSOD activity, and insulin secretion. We therefore sought to determine the metallation status of MnSOD in wild-type mice and whether altering that status affected β-cell function. 129/SvEVTac mice given supplemental manganese exhibited a 73% increase in hepatic MnSOD activity and increased metallation of MnSOD. To determine whether manganese supplementation offered glucose homeostasis under a situation of β-cell stress, we challenged C57BL/6J mice, which are more susceptible to diet-induced diabetes, with a high-fat diet for 12 weeks. Manganese was supplemented or not for the final 8 weeks on that diet, after which we examined glucose tolerance and the function of isolated islets. Liver mitochondria from manganese-injected C57BL/6J mice had similar increases in MnSOD activity (81%) and metallation as were seen in 129/SvEVTac mice. The manganese-treated group fed high fat had improved glucose tolerance (24% decrease in fasting glucose and 41% decrease in area under the glucose curve), comparable with mice on normal chow and increased serum insulin levels. Isolated islets from the manganese-treated group exhibited improved insulin secretion, decreased lipid peroxidation, and improved mitochondrial function. In conclusion, MnSOD metallation and activity can be augmented with manganese supplementation in normal mice on normal chow, and manganese treatment can increase insulin secretion to improve glucose tolerance under conditions of dietary stress.