The Kielin/Chordin-like Protein KCP Can Attenuate High Fat Diet Induced Obesity And Metabolic Syndrome In Mice Model

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Abstract

Obesity and its associated complications, such as insulin resistance and non-alcoholic fatty liver disease, are reaching epidemic proportions in the developed world, primarily due to the increased availability of high caloric foods and the decrease in daily physical activity. It is well established that energy balance is critical for maintaining normal body weight and homeostasis. When caloric intake chronically exceeds energy expenditures, white adipose tissue stores excess energy in the form of triglycerides, leading to obesity and related complications such as type-2 diabetes, a condition also referred to as metabolic syndrome. In mice, the TGF-β superfamily is implicated in the regulation of white and brown adipose tissues differentiation. The KCP protein is a secreted regulator of the TGF-β superfamily pathways that can inhibit both TGF-β and Activin signals while enhancing the Bone Morphogenetic protein (BMP) signaling. However, the effects of KCP on metabolism and obesity have not been studied in animal models. Thus, we examined the effects of KCP loss or gain of function in mice that were maintained on either a regular or a high fat diet. Loss of KCP sensitized mice to obesity and associated complications such as hepatic steatosis and glucose intolerance. In contrast, transgenic mice that expressed KCP in the kidney, liver and brown adipose tissues were resistant to developing high fat diet induced obesity and had significantly reduced white adipose tissue. KCP over-expression was able to shift the pattern of Smad signaling in vivo, to increase the levels of P-Smad1 and decrease P-Smad3, resulting in resistance to high fat diet induced hepatic steatosis and glucose intolerance. The data demonstrate that shifting the TGF-β superfamily signaling with a secreted inhibitor or enhancer can alter the profile of adipose tissue to reduce obesity and can inhibit the initiation and progression of hepatic steatosis to significantly reduce the effects of high fat diet induced metabolic disease. In summary, the results of this suggest that altering TGF-β superfamily signaling pathway by a secreted protein can attenuate renal fibrosis and the negative effects of obesity induced metabolic syndrome. Provide a conceptual basis for the use of secreted protein or derivatives to attenuate profibrotic pathways that depend on continued TGF-β signaling and/or counteraction by BMPs may potentially provide a novel approach to translating the protective role of BMP-7 into clinical benefit.