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Bone Morphogenetic Protein 4 regulates white, beige and brown adipose tissue

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Vita Stråket 12, Sahlgrenska Sjukhuset, Göteborg, fredagen den 9 juni 2017, klockan 13.00

Av Jenny Hoffmann

Fakultetsopponent: Professor Hadi Al-Hasani
German Diabetes Center, Düsseldorf, Tyskland

Avhandlingen baseras på följande delarbeten

I. Gustafson B, Hammarstedt A, Hedjazifar S, Hoffmann JM, Svensson PA, Grimsby J, Rondinone C and Smith U. **BMP4 and BMP antagonists regulate human white and beige adipogenesis.** *Diabetes 2015 May; 64 (5):1670-81*

II. Hoffmann JM, Grünberg JR, Church C, Elias I, Palsdottir V, Jansson J-O, Bosch F, Hammarstedt A, Hedjazifar S and Smith U. **BMP4 gene therapy in mature mice reduces BAT activation but protects from obesity by browning subcutaneous adipose tissue.** *Manuscript under revision*

III. Hoffmann JM, Hammarstedt A, Grünberg JR, Elias I, Palsdottir V, Bosch F, Hedjazifar S and Smith U. **BMP4 gene therapy improves insulin resistance in obese mice without effects on adipose tissue browning or body weight.** *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

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Bone Morphogenetic Protein 4 regulates white, beige and brown adipose tissue

Jenny Hoffmann

Avdelningen för Molekylär och Klinisk Medicin, Institutionen för Medicin, Sahlgrenska Akademin, Göteborgs universitet, Sverige, 2017.

Abstract

Obesity and its associated complications, including Type 2 diabetes, are increasing at an epidemic rate globally. Adipose tissue exerts different functions and is central in energy homeostasis, and it consists of white, beige or brown adipocytes. White adipocytes (in white adipose tissue, WAT) store and release lipids while brown adipocytes (in brown adipose tissue, BAT), oxidize lipids and generate heat. Beige adipocytes reside in WAT, appear white but can oxidize lipids upon stimulation (browning). The aim of this thesis was to investigate the role of Bone Morphogenetic Protein 4 (BMP4) in white, beige and brown fat. In Paper I, we used human WAT biopsies and precursor cells. In Paper II and III, we gave adult mice adeno-associated viral (AAV) vectors to increase circulating BMP4. Endogenous BMP4 is increased in WAT in obesity, and so are BMP antagonists, resulting in reduced BMP4 signalling. WAT browning was enhanced by increasing BMP4 signalling in human precursor cells and in WAT of lean mice. Surprisingly, BAT activity was inhibited in the mice, but whole-body energy expenditure was increased which protected from obesity. However, AAV BMP4 did not enhance browning of WAT in initially obese mice, likely due to the cellular BMP4 resistance. Additionally, all AAV BMP4-treated mice had increased insulin sensitivity. In summary, BMP4 is an important regulator of white, beige and brown fat. BMP4 increases in WAT in obesity but its positive effects are antagonized by the BMP antagonists. However, increasing BMP4 signalling can prevent obesity by browning WAT and also increase insulin sensitivity making it an interesting novel therapeutic target.

Keywords: Obesity, BMP4, browning, WAT, BAT, insulin sensitivity

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