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Abstract 1

Potential Role of the Cardiac Protease Corin in Energy Metabolism

Jingjing Jiang,[1] Yujie Cui,[1] Wei Wang,[1] Qingyu Wu[1,2]

[1]Department of Molecular Cardiology and [2]Department of Nephrology and Hypertension, Lerner Research Institute, Cleveland Clinic, Cleveland, OH

The melanocortin-mediated pathway plays an important role in energy homeostasis. In the brain, the binding of α-melanocyte stimulating hormone (α-MSH) to melanocortin 4 receptor (MC4r) inhibits appetite, thereby reducing food intake and body weight. Agouti and agouti-related protein block α-MSH binding to MC4r and increase appetite and food intake. In mouse skin, agouti also blocks α-MSH binding to melanocortin 1 receptor, promoting yellow pigment formation. Naturally occurring mutations in lethal yellow (A^Y) mice increase agouti protein expression, causing obesity, hypertension, and diabetes.

Corin is a heart enzyme that converts inactive pro-atrial natriuretic peptide (pro-ANP) to active ANP, a cardiac hormone that regulates blood pressure and cardiac function. In mice, lack of corin blocks ANP production and causes hypertension. In humans, corin gene variants are linked to hypertension and cardiac hypertrophy in African Americans. In functional studies, we found that the corin variants impaired biological activities in vitro and in vivo, suggesting that corin defects may contribute to hypertension and heart disease in patients.

Corin is made primarily in the heart. Unexpectedly, corin expression also was detected in the brain and hair follicle. Corin null mice had a more yellowish coat color than that of controls. This effect was agouti gene-dependent. It appears that lack of corin enhances the agouti pathway in mice. We performed cell-based experiments to examine the effect of corin on the expression of a selected set of peptide hormones that are involved in energy metabolism. In HEK 293 cells, co-transfection of a corin plasmid reduced the expression of recombinant agouti and agouti-related protein. In similar experiments, co-transfection of the corin plasmid also reduced the expression of urocortin III but not urocortin I and II. The observed effect of corin on these peptides depended on its catalytic activity, as corin active site mutant had no such an effect in these experiments.

Our results suggest that corin may participate in energy metabolism by down-regulating peptide hormones that control appetite. Currently, we are testing this hypothesis in additional biochemical studies. We also have made corin transgenic mice to examine the effect of corin expression levels on body weight and food intake. These studies should help to identify a potential role of corin in regulating energy metabolism.

* BHBI = Bakken Heart-Brain Institute