Title of Project : Physiological Roles of Mesenchymal cell-Derived Hormones and Their Failures

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Research Area : Medicine, dentistry, and pharmacy

Keyword : Endocrinology

【Purpose, Background of the Research and Research Methods】 Hormones are secreted from endocrine cells, bind to receptors in the target cells, and exert functions. Endocrine system is signal transduction system, the functions of which are reproduction, growth, development, homeostasis, and energy metabolism. Hormones have been regarded to be secreted from epithelial cells in pituitary, thyroid, adrenal and others. Cardiovascular, adipose, and skeletal systems, which consist of mesenchymal origin cells, were regarded to function as organs for pump, energy storage and movement. However, recently, it has been discovered that these organs have also endocrine functions. We have investigated the clinical significance and application of natriuretic peptide family (ANP, BNP and CNP) as cardiovascular hormones, letpin as an adipocytokine, and CNP as a skeletal hormone.

Fig1 Cardiovascular Systems as Endocrine Organs and Cardiovascular Hormones

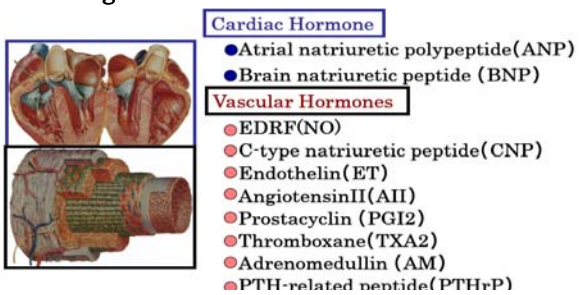


Fig2 Adipose Tissue as the Larges Endocrine Organ and Adipocyte-Derived Hormones

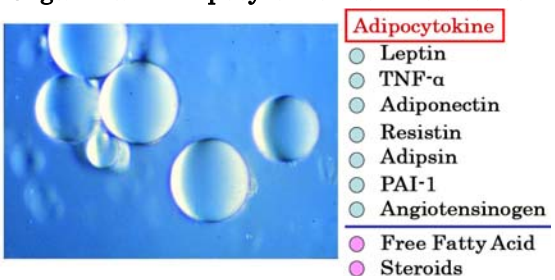
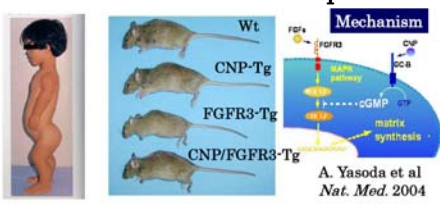


Fig3 Therapeutic Significance and Mechanism of CNP in Achondroplasia



CNP and its receptor, GC-B, are widely expressed in brain, vascular cells, osteochondrocytes and other tissues. Our systemic CNP KO mice have been very difficult to analyze because of severe skeketal phenotype. In order to elucidate significance of CNP/GC-B system in non-skeletal tissues, we will create and analyze tissue-specific CNP KO mice and GC-B KO mice.

Leptin is an anti-obesity hormone. Leptin resistance, the suppression of leptin action in diet–induced obesity, is a critical issue. Obesity induces insulin resistance and disorders of glucose and lipid metabolism, which are summarized as adipotoxicity. In the present study we elucidate leptin resistance and amelioration of adipotoxicity by leptin.

Identification of novel bioactive substance from mesenchymal tissues is also our goal in the present study.

【Expected Research Achievements and Scientific Significance】 The aim is the elucidation of physiological significance and failure of mesenchymal cell-drived hormones. The present study will exploit novel therapies including CNP in achondroplasia and leptin replenishment in generalized lipodystrophy. The present study is expected to clarify significance and clinical application of CNP/GC-B system in tissues other than skeletal system. By contributing to elucidation of leptin resistance and amelioration of adipotoxicity by leptin, the present study will promote the development of novel therapies for common diseases such as diabetes mellitus, metabolic syndrome and obesity as well as rare diseases.

【Publications Relevant to the Project】

・Nakao K. Adiposcience and adipotoxicity. *Nat Clin Pract Endocrinol Metab*.5(2):63 2009

・Yasoda A, Nakao K. et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med*. 10(1):80-6. 2004

【Term of Project】 FY2009-2013

【Budget Allocation】 163,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.kuhp.kyoto-u.ac.jp/~med2/index-jp.html