

Ghrelin: from Discovery to Translational Research

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A complex network of cell-cell communication system by peptide hormones works for maintaining the mammalian homeostatic balance. To further clarify the intricate mechanisms of the regulation, it is important to discover unidentified bioactive peptides. Thus, we have been searching for novel bioactive peptides by using our own methods. In the course of these studies, we discovered three natriuretic peptides (NPs), ANP (1984), BNP (1988) and CNP (1990), from mammalian heart and brain. After that, in 1993, we discovered a novel hypotensive peptide, adrenomedullin (AM), in human pheochromocytoma. These studies elucidated new mechanisms of cardiovascular system controlled by these peptides. Moreover in 1999, we discovered ghrelin, a novel GH-releasing peptide, from rat stomach as an endogenous ligand for the GHS-R, an orphan GPCR. Ghrelin has a marvelous structure modified by fatty acid, n-octanoic acid, which is essential to its activity. Ghrelin is primarily produced in distinct endocrine cells, X/A-like cells, in the stomach. Ghrelin-producing neurones are also present in the hypothalamic arcuate nucleus, a region that regulates GH release and food intake. Beside the stimulatory effect of GH release, ghrelin is also involved in the regulation of feeding, energy metabolism and cardiovascular system. In fact, ICV or IV injection of ghrelin induced potent GH-releasing and appetite-stimulating effects in rats. In the clinical trial, repeated administration of ghrelin improves left ventricular structure and function, exercise capacity, and muscle wasting in patients with chronic heart failure (CHF). Thus, ghrelin also has multifaceted roles in the cardiovascular system and metabolism. In this lecture, I would like to present the discovery process, physiological significance and therapeutic application of ghrelin.