***Japan Academy Prize to:***

Kenji KANGAWA

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for "Discovery of Novel Bioactive Peptides with Special Reference to Ghrelin"

***Outline of the work:***

Mammalian homeostatic balance is maintained by a complicated and elaborate cell-cell communication system, and a breakdown in this control system may lead to disease. In order to better understand this complex system, Dr. Kenji Kangawa has been conducting research to identify novel bioactive peptides and to explore new regulation mechanisms. Although challenging, the discovery of novel peptides can lead to rapid research progress and have an extraordinary impact.

Dr. Kangawa developed a novel method to examine trace amounts of peptides. Using this methodology, he has contributed to the discovery of over 30 novel bioactive peptides. After his early work and discovery of peptides in the brain, he discovered three novel natriuretic peptides in the mammalian heart and brain, namely, atrial natriuretic peptide (ANP; 1984), brain natriuretic peptide (BNP; 1988) and C-type natriuretic peptide (CNP; 1990), and determined their structure. Among them, his successful identification of ANP in the human heart elucidated a new mechanism by which ANP regulates blood pressure and body fluid volume. This novel finding also indicated that the heart is not only a pump but also an endocrine organ involved in cardiovascular regulation. Since this discovery, ANP has become an extremely important molecule in the explosive advancement of research in natriuretic peptides and their clinical application.

In 1993, Dr. Kangawa discovered adrenomedullin, a potent vasodilatory peptide, located in human pheochromocytoma tissue and identified its physiological significance. As a result, he determined that adrenomedullin is closely related to cardiovascular and inflammatory diseases and that it plays a compensatory role in these diseases through a wide variety of physiological functions, including regulation of cardiac function, inhibition of apoptosis, regulation of cell proliferation and anti-inflammatory effects in addition to a vasodilatory effect. Along with ANP and BNP, adrenomedullin is expected to have therapeutic applications.

In addition, following the outcome of this long-term research, Dr. Kangawa discovered and determined the structure of a novel growth-hormone releasing peptide, named ghrelin, in rat and human stomach tissue (1999). At the time of Dr. Kangawa's discovery, it was speculated that an unidentified brain factor stimulates growth-hormone release from the pituitary gland, but research groups worldwide had been unable to isolate this factor for more than 20 years. Dr. Kangawa's discovery of ghrelin in the stomach was groundbreaking as he led the world in identifying this unknown factor. Ghrelin, a 28-amino-acid peptide and a potent stimulator of growth-hormone release, is acylated with the fatty acid, *n*-octanoic acid. This modification is essential for its activity, and ghrelin is the first example of such a bioactive peptide. As post-translational modification of ghrelin, such as fatty-acid modification, cannot be predicted from genomic information, Dr. Kangawa's discovery of ghrelin was very significant post-genome

research because it underscored the importance of determining the molecular structure that functions in the body. In addition to growth hormone-releasing activity, ghrelin is involved in appetite stimulation and energy metabolism regulation as ghrelin is the only feeding signal sent from the gastrointestinal tract to the brain. More recently, it was also revealed that ghrelin has beneficial effects on the cardiovascular system through vasodilation and tissue protection and is also drawing attention as an important anti-aging hormone. As with his previous research, Dr. Kangawa's discovery of ghrelin has pioneered a new field in the regulatory mechanisms in the body.

Dr. Kangawa has received the Takeda Medical Award (2005), the Uehara Award (2006), and other domestic awards for his research accomplishments in bioactive peptides, including the aforementioned ghrelin. He has also received international awards, including the Asia and Oceania Medal (Society for Endocrinology, 2005) and Wertheimer Award (International Association for the Study of Obesity, 2006). Furthermore, Thomson Scientific (US) proclaimed that Dr. Kangawa's research on ghrelin placed him first on the list of natural scientists who have published the largest number of 'hot papers' with an unusually high citation rate (within the top 0.1%) over two years from 2000 to 2001 (eight hot papers). As a speaker, Dr. Kangawa is highly respected worldwide, and he has been invited to give plenary lectures at many international conferences, including the Karolinska Institutet Nobel Conference (2004), where he was the only speaker invited from Japan.

Dr. Kangawa's research started from his original methodology and ultimately led to the elucidation of a novel regulatory mechanism in the body. Although this regulatory mechanism has been difficult to clarify by genome science alone, Dr. Kangawa has elucidated novel mechanisms at the molecular level by identifying endogenous bioactive peptides. Among his accomplishments, his discovery of ghrelin is outstanding. Dr. Kangawa's research on endogenous bioactive peptides has not only elucidated novel regulation mechanisms but also facilitated the development of diagnostic applications and therapeutic drugs that have significantly impacted society.

**Selected original papers**


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