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Novel findings on the functions of non-visual G protein-coupled Receptor Kinases (GRKs): Their marked inhibitory effect on adrenomedullin type 1 receptor signaling

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Adrenomedullin (AM), a potent hypotensive peptide, can powerfully protect against various cardiovascular diseases through the AM1 receptor, which consists of the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein 2 (RAMP2). Of the seven types of G protein-coupled receptor kinases (GRKs), GRK4 and GRK5 are well-known to promote the pathological conditions of hypertension and heart failure. Herein, we examined the effects of the non-visual GRKs, which include GRK2 through GRK6, on the cell-surface expression and signaling of the human AM1 receptor.

We constructed a set of V5-tagged mutants in which the cytoplasmic C-terminal tail (C-tail) of CLR was progressively truncated. We, then transiently transfected these mutants into HEK-293 cells that stably expressed RAMP2.

The cell-surface expression of the wild-type or mutant receptors was quantified by flow cytometric analysis. The ^{125}I-AM binding and AM-induced cAMP production of the receptors was also determined. Of the five GRKs tested, only GRK4 and GRK5 markedly reduced the translocation of the AM1 receptors to the cell surface, thereby abolishing AM binding and signaling; in these cases, no receptor internalization was found. This novel function of GRKs was abrogated by the complete loss of the C-tail of CLR or by the substitution of the entire C-tail of CLR with that of the β_2-adrenergic receptor. Additionally, this function was critically dependent on the Ser-Phe-Ser-Asn-Ser sequence in the C-tail of CLR.

The present findings suggest that the effects of AM may be impaired in circulatory diseases that are involved in the induction of the GRK4 and GRK5 proteins.

Biography

Kenji Kuwasako from 2008-Present: Associate Professor, the Frontier Science Research Center, University of Miyazaki; 2007-2008: Assistant Professor, the Frontier Science Research Center, and University of Miyazaki; 2006-2007: Assistant Professor, Division of Circulation and Body Fluid Regulation, Faculty of Medicine, University of Miyazaki; 2004-2006: Assistant Professor, the First Department of Internal Medicine, University of Miyazaki; 2003-2004: COE Special Researcher, the First Department of Internal Medicine, University of Miyazaki; 2000-2003: Medical Staff in the First Department of Internal Medicine, Miyazaki Medical College; 1998-2000: Guest Researcher, Shionogi Institute for Medical Science, Osaka, Japan.

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