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Design and development of small peptidomimetics of RXFP1 for the treatment of acute heart failure

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Heart disease is the second biggest killer. Human relaxin 2 (H2 relaxin), an insulin-like peptide, passed a phase III clinical trial (in 2012) for its vasodilatory benefits in patients with acute heart failure and serelaxin (recombinant H2 relaxin) was recently (in 2013) granted a "breakthrough therapy" designation by the FDA. The author's group aims to improve this current drug and develop the next generation molecule. In order to maximize its future translational potential, the group will address the three following issues:

1. Large size and complex structure: The size (53 amino acids) and complex structure (two chains, linked by three disulfide bonds) of H2 relaxin represent a considerable challenge for its synthesis limiting modifications of the peptide to optimize its efficacy and stability.
2. Cross-reactivity with other receptors: H2 relaxin exerts its biological actions through its cognate receptor, Relaxin Family Peptide Receptor 1 (RXFP1; initially discovered as LGR7). However, it also activates RXFP2, the native receptor for the related insulin-like peptide 3, INSL3; opening the possibility of potential side-effects through RXFP2-mediated physiological processes.
3. Short half-life in blood: Like insulin, H2 relaxin has a very short half-life. Hence, when injected into patients, H2 relaxin will lose half its activity within 10 minutes because it is degraded by blood enzymes and cleared by the kidney and liver.

Thus, there is an urgent need to design and develop simpler H2 relaxin analogues that are easier to prepare and modify, have high selectivity for RXFP1 and retain their activity for an extended therapeutic time-frame in patients with acute heart failure.

Biography

M Akhter Hossain has completed his PhD at the age of 27 years from Tokyo Institute of Technology and Postdoctoral studies from The University of Melbourne. He is the Head of insulin peptides laboratory at Florey Institutes of Neuroscience and Mental Health, The University of Melbourne, Australia. He has published more than 70 papers in reputed journals including in JACS, PNAS, JMedChem and JBC. He is serving as an editorial board member of two journals including Frontiers in Chemical Biology. His group is interested in therapeutic insulin-like peptide-based drug design and development.

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