Bioactive Conformation of Peptides for Drug Design

Seonggu Ro,[1,*] Dong-Kyu Shin,[1] Young-Ho Jeon,[1] Ki-eun Kim[2] and Chang-Joo Yoon[2]

[1]Biotech Research Institute, LG Chemical Ltd. / Research Park, Taejon 305-380,
[2]Department of Chemistry, The Catholic University of Korea, Pucheon 420-743

Peptides are involved in most of physiological events in human body. To initiate and control such events, they usually bind to corresponding proteins. When a peptide bind to a protein, the peptide is required to adopt a specific conformation corresponding to the binding site of the protein. To date, many studies have shown that the conformation is critical for the bioactivity of peptides. Thus, to identify such conformation is critical for the design of peptidomimetic drugs that have been one of the main focuses in modern drug discovery. This conformation used to be named 'bioactive conformation'. In this presentation, we discuss general methods to identify the bioactive conformation of peptides and our experiences in each method.

1) Bioactive conformation from Constrained Peptidomimemtics

As shown in Fiure 1, constrained peptidomimetics that can show same conformational preference in both free and bound states, are systematically incorporated into the place of pharmacophoric residues. Then, biological assays are carried out. If one of constrained analogs is active, it means that the conformation of the replaced pharmacophoric residue in bound state is the same as a preferred conformation of the constrained peptidomimetic residue incorporated. Thus, bioactive conformations of peptides can be identified by combination of such information

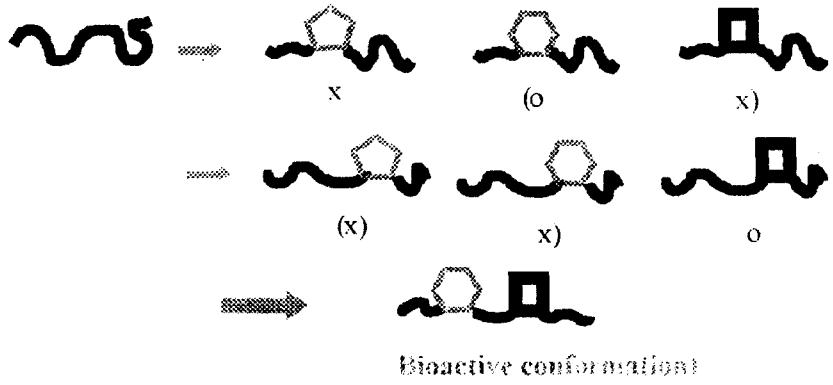

Figure 1. Constrained peptidomimetics approach for the identification of bioactive conformation

2) Bioactive Conformation from the comparison of solution structures

Since recognition of peptides by proteins occurred in solution, one of the preferred solution structures can be the bioactive conformation. Thus, after examination of preferred solution conformations of each analog, the bioactive conformation can be determined as the conformation that is commonly adopted by active analogs and is not adopted by inactive analogs (Figure 2).

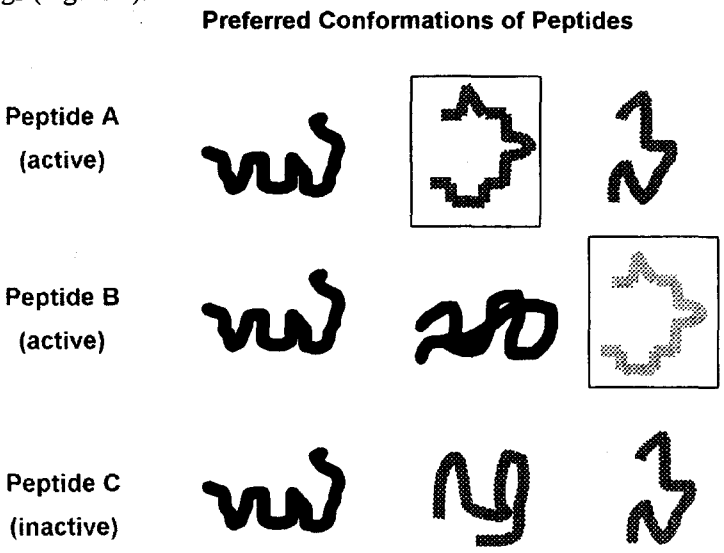

Figure 2. Identification of bioactive conformation from preferred solution conformations.

3) Bioactive conformation from trNOE experiments

In the cases that the interested peptide is highly flexible in solution and can bind weakly to the corresponding protein (~ 1 μM), we can employ transferred NOE (trNOE) experiments. During these experiments, conformational information about the protein-bound state of a peptide is transferred to the unbound state. In combination with 2D-NMR spectroscopy, the transferred NOE (trNOE) experiment has been particularly useful for deriving peptide conformation bound to target proteins.

It is expected that many more biologically active peptides and their functions will be discovered in post-genomic era by the studies of functional genomics and bioinformatics. Thus, to design novel drugs based on the biologically active peptides discovered, efforts to identify bioactive conformation of peptides will increase immensely.