Temperature dictates the conformational preference of "RGD" in peptide sequence "RIPRGDMP" from kistrin and selects the bio-active conformation: Implications for inhibitor design

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The interactions of peptide ligands with proteins face challenges in recognizing binding surfaces due to availability of a multitude of conformations. Therefore it is essential to constrain the peptide for the recognition of receptors and thus finding the bioactive conformation. The cell surface receptor protein family Integrins recognize "RGD" sequence which is present in different proteins. To determine the bioactive conformation required to bind with receptor aIIb_{β3}, the peptide sequence "RIPRGDMP" from Kistrin was inserted into CDR 1 loop region of REI protein (REI-RGD34). It helps out in finding the possible bioactive conformation of peptide by restricting the sampling space. The activity of REI-RGD34 was studied and found that as the temperature increased REI-RGD34 showed a higher affinity towards the receptor aIIbb3. The proposed mechanisms for the increased activity of REI-RGD34 at higher temperature were justified in either of two ways. One, the modified complex forces the restricted peptide to adopt a bioactive conformation or second, it unfolds the peptide in a way that opens its binding surface with high affinity for receptor. In this study we model the conformational preferences of "RGD" sequence in octapeptide alone and in the presentation scaffold at two different temperatures (25[°]C and 42[°]C). We found that at higher temperature "RGD" sequence from "RIPRGDMP" adopt turn conformation, while a bend conformation was observed at low temperature. The analysis of various pharmacophoric parameters hint that turn conformation of "RGD" sequence adopted at high temperature could be the potential bio-active conformation.