In silico designing and creation a new generation of reteplase with more fibrin specificity

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Abstract

Introduction: Reteplase is a fibrin-specific thrombolytic drug and non-glycosylated modified recombinant form of human tissue plasminogen activator (t-PA). It is containing kringle-2 and serine protease domains but the epidermal growth factor and fibronectin finger domains are absent. The lack of finger domain in reteplase cause decrease fibrin specificity. Since the enhancing fibrin specificity is one of the aim for development new thrombolytic drug, due to decreasing side effect such as hemorrhage, also reteplase is non-glycosylated and can be produced in bacterial system at low cost, in this study a new generation of reteplase designed with more fibrin specificity.

Methods and Results: According to the sequence of protein drugs with more fibrin specificity, mutations in reteplase sequence consist of substitution mutation in Kringle 2 domains and adding sequence of mutated finger domain to reteplase sequence. 3D structure of this new reteplase was created by Modeller9.17 software and then simulated by Gromacs 5 software for 20 ns. Docking simulation was performed between new and wild reteplase with fibrin by HADDOCK server separately. The results showed that new reteplase has better interaction with fibrin compared with wild type (table1).

Parameter	Wild reteplase	New reteplase
HADDOCK score*	-35.8 +/- 8.3	-43.2 +/- 21.3

*More negative score is better score

Conclusions: In this study a new generation of reteplase with more fibrin specificity was designed *in silico*. Since the production of reteplase has low cost compared with tPA, improvement its structure to desirable features such as increasing fibrin specificity, can be a way to achieve a favorable thrombolytic drug.

Key words: Thrombolytic drug, Reteplase, Fibrin specificity, *In silico*