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Roza Aisina, Liliya Mukhametova, Sergei Varfolomeyev

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Synergistic fibrinolysis: the combined effects of tissue plasminogen activator and recombinant staphylokinase *in vitro*

Roza Aisina*, Liliya Mukhametova, Sergei Varfolomeyev

Chemical Enzymology Department, Chemistry Faculty, The M.V. Lomonosov Moscow State University, 119992 Moscow, Leninskie gori 1/3, fax: 7(495)939-5417, e-mail: dekanat@chem.msu.ru

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Abstract

Background: Mechanisms of fibrin-specificity of tissue plasminogen activator (tPA) and recombinant staphylokinase (STA) are different, therefore we studied *in vitro* the possibility of the synergy of their combined thrombolytic action.

Methods: Thrombolytic effects of tPA, STA and their combinations were measured by lysis rate of human plasma clot and side effects were evaluated by decreasing in fibrinogen, plasminogen and α_2 -antiplasmin levels in the surrounding plasma at 37°C *in vitro*.

Results: STA и tPA induced dose- and time-dependent clot lysis: 50% lysis in 2 h was obtained with 30 nM tPA and 75 nM STA, respectively. At these concentrations, tPA produced greater degradation of plasma fibrinogen than STA. According to a mathematical analysis of dose-response curves by the isobole method, combinations of tPA and STA caused a considerable synergistic thrombolytic effect. The simultaneous and sequential combinations of tPA (<4 nM) and STA (<35 nM) induced a significant fibrin-specific synergistic thrombolysis, which was more pronounced in 2 h at simultaneous combinations than at sequential addition of STA after 30 min of tPA action. Simultaneous combination of 2.5 nM tPA and 15 nM STA showed a maximal 3-fold increase in thrombolytic effect compared to the expected total effect of the individual agents. Sequential combinations caused a lower depletion of plasma proteins compared to simultaneous combinations.

Conclusions: The simultaneous and sequential combinations of tPA and STA possessed synergistic fibrin-specific thrombolytic action on clot lysis *in vitro*.

General significance: The results show that combined thrombolysis may be more effective and safer than thrombolysis with each activator alone.

Keywords: Staphylokinase, Tissue plasminogen activator, Combination, Synergy, Fibrinolysis, Fibrinogenolysis

Abbreviations: Pg, plasminogen; Glu-Pg, Glu-plasminogen; Lys-Pg, Lys-plasminogen; Pm, plasmin; STA, staphylokinase; Pg·STA and Pm·STA, equimolar complexes of plasminogen·staphylokinase and plasmin·staphylokinase, respectively; proUK, prourokinase; UK,

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