Thursday, July 16, 1981

Poster Presentations

Fibrinolysis – VII

11:00–12:30 h

Huron Room Boards 125–136

0658

COMPLEXING OF LOW M_r-WEIGHT HUMAN UROKINASE IN RAT SERUM AND ITS DEGRADATION INTO FRAGMENTS OF VERY SMALL MOLECULAR WEIGHT IN VIVO BUT NOT IN VITRO.

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Highly purified low molecular weight urokinase (LM_r-UK), moving on SDS-PAGE (reduced and non-reduced) as a single band of 32 kdalton, was labelled with ^{125}I by the chloramine-T method. 10^6 cpm of this ^{125}I-LM_r-UK (94% TCA precipitable) were injected into the inferior vena cava of laparatomized albino rats, which were maintained at 37 °C. Blood samples were collected by cardiac puncture 5, 30 and 90 min respectively after the injection. Serum, obtained from these samples, was fractionated on a Sephadex G-100 column, calibrated with proteins of known M_r. Radioactivity was measured in the collected fractions.

In the 5 min sample, the radioactivity was distributed in 2 peaks, corresponding to 32 kdalton and to > 70 kdalton respectively. In the 30 min sample, the distribution was characterized by a diminution of the 32 kdalton peak and the appearance of a third peak corresponding to a M_r of < 4 kdalton. In the 90 min sample, the LM_r-UK peak had disappeared almost completely. About 40% of the ^{125}I-activity was present in a skewed high M_r peak with a broad maximum in the 85-100 kdalton region; ∿ 60% of the ^{125}I-activity was recovered in late fractions corresponding to < 4 kdalton. In control experiments, pooled rat serum was incubated in vitro with ^{125}I-LM_r-UK for 5, 30 and 90 min respectively and samples were fractionated on the same column. The radioactivity distribution showed only the 32 and > 70 kdalton peaks, but no < 4 kdalton peak.

These results suggest that LM_r-UK is complexed to a carrier protein, both in vivo and in vitro, but that it is degraded into small fragments in vivo only. Attempts to characterize the nature of these complexes are in progress.

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THROMBOLYTIC PROPERTIES OF PURIFIED HUMAN TISSUE PLASMINOGEN ACTIVATOR IN A DOG FEMORAL VEIN THROMBOSIS MODEL.

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Experimental thrombosis was produced in an isolated 4 cm section of the femoral vein in the groin region of beagle dogs using a mixture of ^{125}I-labeled human fibrinogen (6×10^6 cpm), dog blood, thromboplastin and thrombin. Saline, 1,000,000 IU of urokinase or 100,000 Units (1 mg) of highly purified tissue plasminogen activator (isolated from the culture fluid of human melanoma cells) was infused intravenously over four hours. The extent of thrombolysis was calculated from the difference between the radioactivity introduced in the clot and that in the recovered clot six hours after the start of the infusion.

In four control animals thrombolysis was 31.0 ± 3.0% (mean ± S.D.). Infusion of urokinase in 3 dogs resulted in 42.7 ± 14.3% lysis. In 5 dogs receiving plasminogen activator thrombolysis was 65.6 ± 21.6%. During infusion the blood radioactivity rose significantly (from 2.5 to 6.6% of the total) in the tissue plasminogen activator group; only a slight rise was observed in the urokinase group and a progressive decline in the control group.

Neither in the controls nor in the tissue plasminogen activator treated animals significant activation of plasminogen, consumption of α_2-antiplasmin or fibrinogen breakdown occurred and no major bleeding was noted. Infusion of urokinase, however, resulted in systemic activation of the fibrinolytic system with extensive fibrinogen breakdown causing a significant bleeding tendency.

It is concluded that in the experimental model used human tissue plasminogen activator has higher specific thrombolytic and a lower systemic fibrinogenolytic effect than urokinase.

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