Thromboplastic and Fibrinolytic Activity of Human Synovial Membrane and Fibrous Capsular Tissue.* (23898)

TAGE ASTRUP AND KNUD-ERIK SJØLIN
Biological Institute, Carlsberg Fn., Copenhagen, and Institute of Pathological Anatomy, University, Copenhagen, Denmark

The balance between clot formation and fibrinolysis regulates local hemostasis(1). We have therefore investigated the thromboplastic and fibrinolytic activities in the human synovial membrane and fibrous capsular tissue to elucidate their role in intra- and periarticular hemorrhage.

Materials and methods. Thromboplastic activity: Fresh tissue (100 mg) was suspended in 0.9% NaCl (0.90 ml) in a Potter homogenizer and stored at −20°C for a few days. After thawing and retreatment in the homogenizer, coarse particles were removed by filtration through cotton wool. Serial dilutions were prepared and clotting times (at 37°C) estimated in mixture consisting of 0.2 ml fresh rabbit citrate plasma, 0.5 ml 0.9% NaCl and 0.1 ml of tissue suspension, after recalcification with 0.2 ml 0.030 M $CaCl_2$ solution. For comparison the activity of a suspension of human brain (as used in Owren's P-P method for estimation of prothrombin activity) was simultaneously estimated. *Fibrinolytic activity*. The amount of plasminogen activator in tissues was estimated according to the principle recently described (2), but with minor modifications since the activities were low and a quantitative extraction of the active principle was not required. Fresh tissue (100 mg) was thoroughly disintegrated in a Potter homogenizer with 2 M KSCN (3.0 ml) followed by slow shaking for 2 hours. After centrifugation the supernatant was diluted with 7 volumes of H_2O and N HCl was added until pH 1 was obtained. After standing for 15 minutes and centrifuging, the precipitate was redissolved in 1 ml 2 M KSCN by neutralization (litmus paper) with solid $NaHCO_3$. This solution was 3 times concentrated with respect to original solution. In some cases, the high lipid content of the tissue sample prevented complete sedimentation by centrifugation and the suspension obtained after first centrifugation was used without additional acid precipitation. Activity was estimated by the fibrin plate method(3) (0.1% bovine fibrinogen) and compared with standard preparation of plasminogen activator from pig heart tissue as previously described (2). *Tissues*: Samples of synovial membrane and of fibrous capsular tissue were obtained from knee joints of 10 persons dying from diseases unrelated to the joints.

Results. None of the samples investigated showed more than a trace of *thromboplastic activity*. Most samples of fibrous tissue had no activity, the rest only traces, and this result could not be caused solely by incomplete dispersion of the fibrous tissue. The synovial tissue was easily dispersed but nonetheless showed only traces of thromboplastic activity. This is demonstrated in Fig. 1, typical of the whole series. It is seen that synovial tissue has only a few per cent of activity of brain suspension used for comparison.

All samples showed *fibrinolytic activity* caused by a tissue activator of plasminogen. This is a stable activator different from the activator found in blood(4). Fig. 2 is an example of an estimation. By interpolation on the standard curve the concentration is 180 units/g synovial tissue and 60 units/g of fibrous tissue. This is in the low (or medium) range of activities found in human organs(5). There were great individual variations, similar to those observed previously (5,6). As mentioned, difficulties were encountered in some estimations. The following additional values were all obtained after the complete procedure (units/g): Synovial tissue: 63, 57, 46, 25, 185; Fibrous tissue: 25, 25, 35, 12, 114.

Discussion. Since no or only slight throm-

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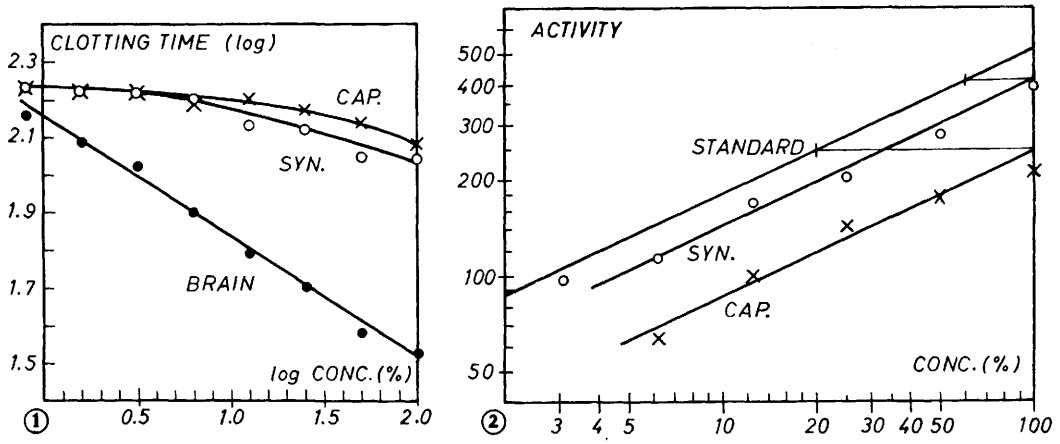

FIG. 1. Thromboplastic activity of human synovial tissue (Syn.) and fibrous capsular tissue (Cap.). *Abscissa:* Logarithm of conc. (in % of stock solution). *Ordinate:* Logarithm of clotting time (sec.). A standard preparation of human brain is used for comparison.

FIG. 2. Plasminogen activator in human synovial tissue (Syn.) and fibrous capsular tissue (Cap.). (Same patient as in Fig. 1.) *Abscissa:* Logarithm of conc. (in % of stock solution). *Ordinate:* Logarithm of activity (product of diameters in mm^2 of lysed zones). A standard preparation of pig heart is used for comparison (30 units/ml).

boplastic activity is present in joint tissues (synovial and fibrous capsular tissue) it is apparent that local hemostasis, after injury of a joint, must be effected chiefly by activation of the plasma thromboplastin system. Subsequent removal of clotted fibrin can then be caused by an effect of the plasminogen activator found in the tissues. This explains why, after hemorrhage in a joint, blood can normally be emptied in fluid condition after a few days.

The high latent activity of the plasma thromboplastin system in normal persons secures normal clotting and hemostasis even at sites where the amount of tissue thromboplastin in the injured tissue is low. In patients with hemophilioid disorders, especially classical hemophilia (AHF deficiency) and Christmas disease (PTC deficiency), bleedings in joints are characteristic symptoms. This can now be easily explained by lack of thromboplastic activity in joint tissues together with deficiency in plasma thromboplastin system occurring in these patients.

Since the defective plasma thromboplastin system can prolong extravasation of blood at sites where the amount of tissue thromboplastin released from injured tissue is low, this can give rise to increased formation of clots which are difficult to dissolve completely again by available amount of fibrinolytic agents. After organization the final result would be a formation of excess of connective tissue. The frequent occurrence of crippling of joints after hemarthrosis in hemophilic patients is an example of this sequence of events, and is in good agreement with experimental findings reported here.

As pointed out recently(7), occurrence of arteriosclerotic lesions in hemophilic patients can be explained on the basis of balance between fibrin deposition and fibrinolysis. The results presented here demonstrate the usefulness of this concept in explaining pathological processes(1).

Summary. 1. Human synovial tissue and fibrous capsular tissue contain no or only traces of tissue thromboplastin. An activator of plasminogen of the tissue type is present in low (but varying) concentrations in both tissues.

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