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133. A Relation between Placental Protein 5 (PP5) and Cagulation and Fibrinolytic Activities during Placental Separation

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Recent reports have indicated that PP5 (Bohn) can be related to the coagulation and fibrinolytic systems during pregnancy. In this paper, we attempted to investigate effects of PP5 on mechanism of blood flowing in the placental circulation and hemostatic mechanism during placental separation, thereby comparing with levels of other clotting and fibrinolytic factors during pregnancy and delivery.

Results:

1) FDP, UKI and PP5 levels were much higher in the retroplacental blood than in the peripheral blood during delivery.

2) PP5 was found to inhibit the activity of plasmin. Although PP5 showed no UK inhibitory activity, PP5 has been mixed into the placental UK inhibitor (Kawano).

3) PP5 inhibits the platelet aggregation induced by ADP and collagen.

4) In severe toxemia of pregnancy, the concentrations of PP5 usually increased.

5) PP5 is enzyme-immunohistochemically located not only in the syncytium, but also around placental infarct and intervillous thrombosis.

In conclusion, PP5 might work on maintenance of blood flowing in the placental circulation and hemostasis after placental separation.

134. Effects of Heparin on Coagulation, Fibrinolysis, and Serum Lipids in Patients with Toxemia of Pregnancy

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It is known that pregnant women with severe toxemia of pregnancy are associated with hypercoagulability and hyperlipemia. On the other hand, it is said that heparin had anticoagulant and lipemia-clearing action. We examined the coagulation, fibrinolysis, and serum lipids before and after subcutaneous heparin administration in 12 pregnant women with severe toxemia, who had gestosis index 4 or more.

Heparin (200 U/kg, twice/day, S.C.) was administered after overnight fast, and blood samples were obtained before and after the administration. We determined PT, APTT, fibrinogen (Fib), antithrombin-III (AT-III), plasminogen, serum FDP, platelet count, platelet aggregation, cholesterol (Chol), triglyceride (TG), HDL-Chol, lipo-protein fractions, and apoproteins (A-I, A-II and B). The results were as follows:

1) APTT is prolonged 1.5-2 times at 3h and 24h after heparin administration ($P<0.005$).

2) AT-III increased at 3h after heparin administration ($P<0.01$).

3) As for serum lipids, Chol, and TG decreased at 3h and 24h, and HDL-Chol increased at 3h after heparin administration.

4) PT, Fib, plasminogen, FDP, platelet count, platelet aggregation, lipo-protein fractions and apoproteins had no remarkable changes.

These results suggest that heparin may be useful for the toxemia of pregnancy.

135. Studies on the Placental Coagulation Inhibitor

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The placenta contains such thrombotic factor as tissue thromboplastin and placental urokinase inhibitor. On the other hand, there are some antithrombotic agents as placental plasminogen activator and platelet aggregation inhibitor.

We isolated another antithrombotic factor from the placenta and some results were obtained as follows:

1) The placental coagulation inhibitor (the inhibitor) was isolated from the human placental microsome, of which tissue thromboplastin activity was removed by delipidation and Con A chromatography.

2) By chromatographic procedures with DEAE-Sephacel, Sephacryl S-300, and Sephadex G-100, this inhibitor was purified finally as a single band on polyacrylamide gel electrophoresis.

3) The inhibitor was a protein, having a molecular weight of approximately 45,000 daltons.

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4) Immunological examination revealed that the inhibitor was different from such well-known anticoagulants as AT-III, α_1-AT, α_2-M, C_1-INA, and has no heparin like characteristics.

5) The inhibitor had neither fibrinolytic nor antifibrinolytic activity.

6) By incubation with this inhibitor, tissue thromboplastic activity was completely inactivated in the extrinsic pathways.

136. Preeclampsia and Antithrombine III

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The significance of measurement of plasma AT III in preeclamptic patients and the human AT III concentrate product supplemental therapy were evaluated. In 39 cases of the preeclampsia, the mean plasma AT III value was 25.9 ± 5.04 mg/dl (28.24 ± 4.38 mg/dl in 22 mild cases, 21.49 ± 2.82 mg/dl in 17 severe cases), and that of 36 normal pregnancy control was 31.65 ± 3.26 mg/dl, in last third trimester. The plasma AT III did not show any deviations throughout the pregnancy course in the normal control, on the other hand, tendency of decreasing of AT III value was observed in the last third trimester. Furthermore, the degree of reduction in plasma AT III value was correlated with severity of disease. Administration of concentrated human AT III was performed to the 8 preeclamptic cases, of which in 4 cases improvement in the mean blood pressure was observed, and in the 5 cases improvement in the albuminuria was observed.

137. Inhibitory Effect of Placental Extracts on ADP-induced Platelet Aggregation

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Purpose: ADP-induced platelet agglutination is especially important as an initial reaction in hemostasis and thrombus formation. In the present study, specific inhibition of ADP-induced platelet agglutination by human placental extract was demonstrated. Since this action was also found in the placental leucine aminopeptidase (P-LAP), the relationship with this enzyme and significance was examined as reported below.

Method: 1) The placenta was solubilized and purified by treatment with Triton-X-100, zinc sulfate, DEAE-cellulose chromatography, hydroxyapatite chromatography and Sephacryl S-300 gel filtration in order to obtain crude P-LAP fraction. Further purification was accomplished through affinity chromatography with Con A-sepharose and ADP-agarose, and Bestatin AH-sepharose chromatography. The fraction with as inhibitory action on ADP-induced platelet agglutination was analyzed by 7% polyacrylamide electrophoresis. 2) The time required for thrombus formation• was measured by the Chandler loop method using 0.1 ml crude P-LAP and 10 ml whole blood. 3) The preventive effect on sudden death in mice in response to intravenous injuction of ADP solution was evaluated. 4) The platelet agglutinability was estimated by measuring the maximal platelet aggregation rate obtained by the addition of f.c. 2×10^{-6} M ADP and f.c. 1 μg/ml collagen to human PRP adjusted to platelet concentration of $3 \times 10^4/\mu$l in NKK-HEMA-TRACER-1.

Results: 1) Crude P-LAP, in the process of purification after isolation from placental extract and P-LAP purified by means of Bestatin AH-Sepharose, specifically inhibited ADP-induced platelet aggregation. The purified final fraction exhibited a single band on electrophoresis. 2) No significant difference was noted in the time required for thrombus formation measured by the Chandler loop method between the Group treated with P-LAP and the Control Group. 3) Pretreatment with P-LAP in mice slightly inhibited sudden death due to ADP administration.

Original Contribution: Clinical application of inhibitors for ADP-induced platelet aggregation found in human placental chorionic tissue was evaluated.

138. Studies on Placental Plasminogen Activator (PPA)

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We've reported the existence of plasminogen activator in placenta, which is combined with its inhibi-

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