It was thought at first that DMSO may have been acting as weak decarboxylase inhibitor but this idea was discarded in view of the following findings: a) No marked penetration of 5-HTP was seen when the amine was dissolved in DMSO indicating no peripheral decarboxylase inhibition. b) When DMSO is given 1 h prior to L-dopa, no penetration of the latter is seen, indicating no reduction in peripheral decarboxylase activity.

The thought that DMSO may have reacted chemically with L-dopa to produce a dopa analogue capable of partially crossing the BBB was also excluded since a) DMSO is a relatively inert chemical compound, b) increase in tubero-infundibular fluorescence was noted following DMSO:L-dopa, c) dopa analogues do not normally fluoresce in tissue using this technique, d) neostrital fluorescence was also increased following DMSO: L-dopa.

It would appear from the above findings, therefore, that DMSO is able to transport L-dopa across the blood brain barrier to some extent. This carrier activity is probably rapid, since any reasonable amount of L-dopa in the brain capillaries is quickly converted by dopa decarboxylase to dopamine, a substance that does not cross the blood brain barrier.

The findings may offer an alternative possibility for increasing dopamine levels in neostrital structures as opposed to massive doses of L-dopa alone or decarboxylase inhibition followed by L-dopa[9]. This increase in brain dopamine is of particular interest in the treatment of Parkinson's disease.

Résumé. Le passage de la dopa à travers la barrière hémato-encéphalique semble être facilité par le diméthyl sulphoxyde (DMSO) tandis qu'aux mêmes conditions le 5-HTP franchit cette barrière seulement dans une région très limitée de l'hypothalamus, chez les rats.

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Plasma Kininogen in Extracorporal Circulation and the Influence of a Protease Inhibitor from Bovine Lung

It is well known that, in extracorporal circulation with heart-lung machine, blood clotting system and fibrinolysis are activated. The relationship of blood clotting system and fibrinolysis to the kininogen kinin system (EISEN[1]) suggests also an activation of the kinin forming system in extracorporal circulation. This paper is concerned with the changes of plasma kininogen level in extracorporal circulation and the influence of the kallikrein-trypsin-inhibitor Contrykal®.

Material and methods. The studies have been carried out in 14 patients (5–44 years old). In these patients open heart surgery with heart-lung machine was performed (12 atrial septal defects, 2 stenosis of the pulmonal valvula). The average perfusion time was 65 min in the range of 35–105 min. We used a heart-lung machine developed by STRUSS and SCHOBER[2]. The blood was carried with a pump of the DE BAKEY-Type with a maximal perfusion volume of 6000 ml per min. The oxygenization was performed with a disc-oxygenator of Kay-Cross. The perfusion was carried out in hypothermia (30–32 °C) with the aid of a heat-exchanger of GÜNDEL[3]. The heart-lung machine was filled with heparinized fresh blood (2500 IU Heparin-Richter® Budapest per 500 ml blood), low molecular dextran preparation (Infukoll M 40® VEB Serumwerk Bernburg) and a glucose solution of 5%. Per litre haemodilution (25 ml per kg) 5000 IU Heparin were added. 500 IU Heparin per kg were given to the patient. The action of Heparin was inhibited with protamin-titration after perfusion was finished. The blood conducting parts of the heart-lung machine used by us were not siliconized.

For the determination of plasma kininogen the blood was taken from patients from the cubital vein with a siliconized and heparinized syringe, from the extracorporal circuit into a siliconized tube. The time course of drawing the samples was as follows: 1 day before operation (taken from patients), 5 min of perfusion, 30 min of perfusion, 60 min of perfusion, 2 h after per-

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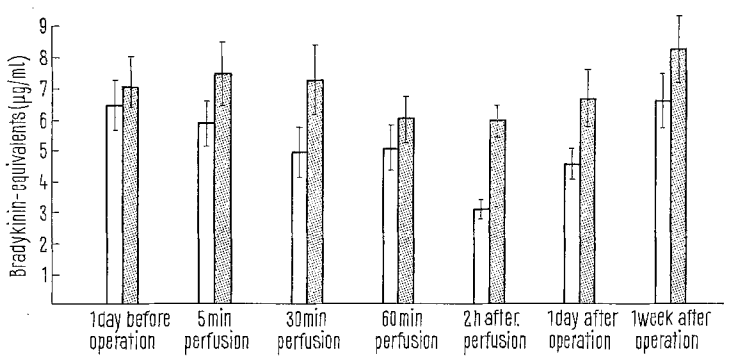

Plasma kininogen during and after extracorporal circulation. Abscissa: time. Ordinate: Kininogen in bradykinin-equivalents µg/ml. White columns: without protease inhibitor. Black columns: with protease inhibitor. Vertical bars are standard error of mean.

fusion, 24 h and 1 week after operation (taken from patients). The plasma kininogen was estimated with the method of DINIZ and CARVALHO[4]. The biological activity of the samples was calculated with the 4-point method on the isolated guinea-pig ileum. Synthetic bradykinin (VEB Berlin-Chemie[5]) was used as standard. The concentration of plasma kininogen is expressed in µg bradykinin per ml plasma released by trypsin incubation (BEq µg/ml).

The first series (8 patients) did not get any protease inhibitor. The second series (6 patients) were treated with the kallikrein-trypsin-inhibitor Contrykal® (VEB Arzneimittelwerk Dresden). The inhibitor activity of this protease inhibitor is expressed in anti-trypsin-units (ATrU). 1 ATrU inhibits the activity of 1 trypsin-unit (according IUB). In the starting of perfusion 20,000 ATrU Contrykal® were given into the heart-lung machine, 20,000 ATrU were administered to the patient during the perfusion and 20,000 ATrU Contrykal® were applicated to the patient after perfusion was finished.

The student-*t*-test was used in the statistical evaluation of the data (p 1%). All values are expressed as mean plus or minus standard error of mean.

Results. First series – without protease inhibitor. After a perfusion time of 5 min the kininogen content of plasma is not significantly different from the value 1 day before operation. During 30–60 min of perfusion the kininogen level drops but not to a significantly different level compared with the value of 5 min perfusion. However, 2 h after perfusion is finished, the plasma kininogen reaches a level which is significantly lower than the level after 5 min perfusion. 24 h after operation the initial kininogen content is regained (Figure).

Second series – with protease inhibitor. The kininogen content of plasma does not change significantly during and after extracorporal circulation. The kininogen values of the first and second series are significantly different 2 h after perfusion is finished (Figure).

The decrease of plasma kininogen level during and after extracorporal circulation and the prevention of kininogen depletion with the protease inhibitor refer to an activation of the kinin-forming system in extracorporal circulation. The mechanism of kinin formation may be related to the activation of fibrinolysis and blood clotting system in extracorporal circulation. It can be supposed that the common link which initiates each of these processes is the Hageman factor. The Hageman factor, activated by contact of blood with glass and other adsorbing surfaces, activates not only plasminogen and plasma thromboplastin antecedent but also the kinin-forming system (MARGOLIS[6], WEBSTER[7]). The kinin formation in this condition can be achieved both by activation of kallikreinogen induced by Hageman factor and plasmin and by the proteolytic action of plasmin on kininogen (EISEN[8]).

Besides the activation of Hageman factor, another mechanism of kinin formation can be discussed. TICE et al.[9] suggested, as a cause of increased fibrinolysis during hypothermic perfusion in open-heart surgery, the activation of lysosomal hydrolytic and proteolytic enzymes. Lysosomal kininogenases may also influence the plasma kininogen content in extracorporal circulation in cases of hypothermia.

A decrease of the plasma kininogen level was found by GOMAZKOV[10] in experiments on rabbits during blood perfusion through glass cuvettes. Using siliconized cuvettes no change of plasma kininogen could be observed. The author discussed kinin formation induced by glass contact as the cause of the fall of systemic blood pressure, blood pH and body temperature in his experiments. But it seems difficult to recognize whether kinins play a role in the very complex haemodynamic changes during and after extracorporal circulation. However, as described in this paper, treatment with a kallikrein-trypsin-inhibitor could be of use not only for inhibition of fibrinolysis (MAMMEN et al.[11]) but also for prevention of decrease of kininogen in extracorporal circulation.

Zusammenfassung. Beim extrakorporalen Kreislauf mit der Herz-Lungen-Maschine wurden die Veränderungen des Kininogengehalts im Plasma und ihre Beeinflussbarkeit mit einem Proteasen-Inhibitor untersucht. Der beobachtete Abfall des Kininogenspiegels im Plasma während und nach der Perfusion und die Hemmung der Kininogendepletion mit dem Proteasen-Inhibitor sprechen für eine Aktivierung des Kininogen-Kinin-Systems im extrakorporalen Kreislauf. Beziehungen zur Aktivierung des fibrinolytischen Systems werden angenommen.

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Bronchodilator Activity of Prostaglandin E_2 when Administered by Aerosol to Three Species

The prostaglandins are a series of hydroxy unsaturated fatty acids widely distributed throughout body tissues. Depending upon the species, pharmacologic preparation, and type of compound studied, the prostaglandins can either stimulate or inhibit bronchial smooth muscle[1].

The bronchodilator properties of aerosolized prostaglandin E_2 (PGE_2) became evident through our observation that it could protect guinea-pigs from a histamine-induced bronchoconstriction[2]. The present study evaluates the response of 3 species to the bronchodilator properties of this compound.

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