

Friday, July 17, 1981

Poster Presentations

Anticoagulants – I

11:00–12:30 h

Grand Ballroom Lobby Boards 201–208

0929

ON THE PHARMACOLOGY OF HIRUDIN. F. Markwardt.
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Hirudin, the anticoagulant substance obtained from medicinal leeches, was isolated and chemically characterized by us 20 years ago. In order to estimate the potential therapeutic effect, its pharmacodynamic and pharmacokinetic properties were studied in animal experiments. Pure hirudin is well tolerated and, except its anticoagulant effect, it proved to be a pharmacologically inert substance. According to its physico-chemical properties as a polypeptide (MW 7600) it is not absorbed enterally in active form and does not penetrate the skin. After parenteral administration hirudin distributes in extracellular fluid. It is eliminated with a half-life of 70 min and 80 % are excreted in unchanged form through the kidneys.

The specific inhibition of thrombin by hirudin in the blood prevents not only fibrinogen conversion but also the thrombin-catalyzed activation of other clotting factors and platelets. The antithrombotic effect was demonstrated in experimental animals (rat, rabbit, dog). The incidence of venous clotting thrombi induced by stasis and of arterial deposition thrombi induced by lesion of the vessel wall was prevented. Of special importance is the effect of hirudin to prevent microthrombosis in DIC induced by infusion of thrombin or endotoxin. In this case hirudin is superior to heparin.

Pre-clinical testing showed that hirudin is a potential antithrombotic agent.

0930

ANTICOAGULANT AND ANTITHROMBOTIC PROPERTIES OF D-PHE-PRO-ARG-H /1/, BOC-D-PHE-PRO-ARG-H /2/, BZ-D-ALA-PRO-ARG-H /3/ AND β -D-PHENYL-LACTYL-PRO-ARG-H /4/. D. Bagdy, É. Barabás, S. Bajusz, E. Széll and I. Bodor. Institut for Drug Research, Budapest, Hungary, Europe.

A series of tripeptide derivatives was synthesized and studied for blood clotting inhibition in vitro and in vivo experiments. Whole blood clotting time /WBCT/, activated partial thromboplastin time /APTT/, thrombin time /TT/ and prothrombin time /PT/ were measured in Thrombelastograph and Coagulometer, resp. using heparin and hirudin as reference substances. The inhibition by /1-4/ of platelet aggregation /PA/ was tested in Chrono-Log Aggregometer. The anticoagulant action of /1-4/ in vivo was investigated in mice, rats, rabbits, dogs and monkeys, resp. by different ways of administration. /1/ was found to be a non competitive inhibitor of thrombin according to Dixon plots / $K_i = 7.5 \times 10^{-8}$ M/. /1-4/ inhibited the thrombin-induced PA specifically. By giving to animals i.v., i.m., s.c. and orally, resp. /1-4/ proved to be effective in all species and the anticoagulant action was dose dependent. In the course of continuous i.v. infusions to conscious rabbits and narcotized dogs, resp. /3-4 mg pro kg/hr for 3 to 6 hrs / WBCT, APTT and TT prolonged to 3-5 times of the starting values. The anticoagulant effect appeared 15 min after starting and returned to normal within 1-2 hrs after stop the infusions. No change either in blood pressure or in respiration could be observed during the infusions. ED₅₀ and LD₅₀ of i.v. infusion in conscious rabbits was found to be 1.3 and 58 mg, resp.. Our results suggest that /1-4/ represent powerful anticoagulant and antithrombotic effects and can be regarded as a new type of anticoagulants.