J. Enzyme Inhibition, 1995, Vol. 9, pp. 1–2
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SYNTHETIC LOW-MOLECULAR WEIGHT THROMBIN INHIBITORS: THE IDEAL ANTITHROMBOTIC DRUG? AN INTRODUCTION

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(Received 8 August 1994)

Very recently, J.J. Sixma and P.G. de Groot discussed various criteria for an ideal antithrombotic drug using as examples new antithrombotic agents that are currently under development.[1] It was postulated that "an ideal antithrombotic drug should inhibit thrombosis without affecting hemostasis. It should have a long half-life. It should be absorbed after oral administration; it should be safe and it should have a wide therapeutic range." When considering the current therapeutically used anticoagulants (e.g. coumarins, heparin and LMW-heparins, aspirin and ticlopidin), they meet some but not all of these various criteria. This has contributed to the active search for other anticoagulant agents, such as inhibitors of clotting factors, (activated) protein C, platelet function inhibitors and antiadhesive compounds.

Today, research is particularly intensive in the field of thrombin inhibitors.[2] It has been shown that direct thrombin inhibitors, both naturally occurring as well as synthetic inhibitors, reveal a number of advantages over the known, therapeutically used anticoagulants in experimental animal models of thrombosis and haemorrhagic risk.[3,4]

Furthermore, thrombin inhibitors inactivate clot-bound thrombin[5] as well as soluble thrombin. Probably, the most important advantage of direct thrombin inhibitors, however, is their ability to immediately neutralize the generated thrombin upon vascular injury. It has been calculated that a pulse of thrombin is formed reaching a peak of about 200 nmol/l[6,7] similar to that demonstrated experimentally in plasma.[8] There are already various thrombin inhibitors available, the potency and specificity of which is sufficient to immediately inhibit such an amount of thrombin.[9] From this point of view, both the naturally occurring thrombin inhibitor hirudin and the synthetic peptide hirulog are quite ideal anticoagulants. However, due to their peptide structure, these agents can only be administered by the parenteral route.

As a matter of fact, in contrast to large peptides and recombinant proteins, only synthetic, low-molecular weight inhibitors will be able to be absorbed after oral

application. Some approaches have already been made with different types of small inhibitors. Boroarginine compounds,[4,10] D-Phe-Pro-Arg-based argininals[11] and benzamidine derivatives[12] show some oral bioavailability, however, they are eliminated relatively quickly from the circulation. Therefore, further research has to focus on the design of inhibitors with a better pharmacokinetic behaviour.

Another problem not definitely solved so far with hirudin is the development of an accepted antidote necessary to cope with haemorrhagic complications after accidental overdosage. As recently shown for benzamidine,[13] it has to be assumed that complexation of small molecules with artificial receptors is accomplished easier than that of large peptides.

Therefore, a synthetic, low-molecular weight inhibitor, selective towards thrombin with a sufficient half-life in the circulation after oral application could be the ideal anticoagulant, leading to a decisive progress in prophylaxis and therapy of thrombosis. All synthetic, low-molecular weight thrombin inhibitors currently under investigation meet to a more or less pronounced extent some of the criteria mentioned above. It will, however, require a lot of additional effort to design the ideal antithrombotic drug for the benefit of mankind.

References

1. Sixma, J.J. and de Groot, P.G. (1992) *Thromb. Res.*, **68**, 507–512.
2. Maffrand, J.P. (1992) *Nouv. Rev. Fr. Hematol.*, **34**, 405–419.
3. Markwardt, F. (1988) *Nouv. Rev. Fr. Hematol.*, **30**, 161–165.
4. Tapparelli, C., Metternich, R., Ehrhardt, C. and Cook, N.S. (1993) *Trends Pharmacol. Sci.*, **14**, 366–376.
5. Weitz, J.I., Hudoba, M., Massel, D., Maraganore, J. and Hirsh, J. (1990) *J. Clin. Invest.*, **86**, 385–391.
6. Walz, D.A., Anderson, G.F., Ciaglowski, R.E., Aiken, M. and Fenton II, J.W. (1985) *Proc. Soc. Exp. Biol. Med.*, **180**, 518–526.
7. Scully, M.F. (1992) *Semin. Thromb. Hemost.*, **18**, 218–223.
8. Hemker, H.C., Wielders, S., Kessels, H. and Beguin, S. (1993) *Thromb. Haemostas.*, **70**, 617–624.
9. Stone, S.R. and Tapparelli, C. (1994) following paper.
10. Hussain, M.A., Knabb, R., Aungst, B.J. and Kettner, C. (1991) *Peptides*, **12**, 1153–1154.
11. Bajusz, S., Szell, E., Bagdy, D., Barabas, E., Horvath, G., Dioszegi, M., Fittler, Z., Szabo, G., Juhasz, A., Tomori, E. and Szilagyi, G. (1990) *J. Med. Chem.*, **33**, 1729–1735.
12. Stürzebecher, J., Prasa, D., Bretschneider, E., Bode, W., Bauer, M., Brandstetter, H., Wikström, P. and Vieweg, H. (1993) *DIC — Pathogenesis, Diagnosis and Therapy of Disseminated Intravascular Fibrin Formation*. (G. Müller-Berghaus, K. Madlener, M. Blombäck and J.W. ten Cate, eds.) pp. 183–190. Amsterdam, London, New York, Tokyo: Excerpta Medica.
13. Bell, T.W. and Santora, V.J. (1992) *J. Am. Chem. Soc.*, **114**, 8300–8302.

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