isozymes, are widely used in the treatment of several types of physiological disorders. In particular, data sets for these sulfonamides, namely, acetazolamide, methazolamide and amuulf, are examples of the selective inhibitors which should exhibit high activity for the corresponding enzyme of the human host. The design of selective active site inhibitors is difficult because the active site of an enzyme is usually well conserved in the course of evolution. In contrast, selective inhibition may be easier if the enzyme misses use of a large cofactor. A substantial part of such a cofactor is not directly involved in the catalytic reaction, and as a consequence, its environment is best conserved. We wondered whether the adiponectin portion of NADP would be a good lead for trypanosomal glycerol-phosphate dehydrogenase (GAPDH) and inhibitor design.

Careful comparison of the Trypanosoma brucei (T.) GAPDH structure, obtained from Laue diffraction study at 3.2 Å, and a 2.4 Å resolution human GAPDH structure reveals: (1) the presence of a small hydrophobic pocket next to the adenine C2-position in T. GAPDH versus the presence of Aen in human GAPDH; (2) the proximity of a hydrophobic canyon next to O2' of the adenine ring in T. GAPDH versus this region being occupied by protein atoms in human GAPDH due to a different loop conformation; (3) the presence of a hydrophobic patch near the adenine C8-position in both T. and human GAPDH.

After one design-synthesis-testing cycle starting from adenosine the following preliminary results were obtained: (1) a 2-methyl adenine substitution improves inhibition 43-fold in T. and 18-fold in human GAPDH; (2) 2'-benzoic acid-2'-deoxy-adenosine selectively inhibits parasite GAPDH and shows a 16-fold better inhibitor; (3) an 8'-benzylic moiety enhances inhibition 100-fold for parasite GAPDH and 50-fold for mammalian GAPDH. More recently, a mica-methoxy benzamide derivative of 2'-deoxy-2'-amino adenosine appeared to have a 170-fold higher affinity for the parasite enzyme and a 5-fold lower affinity for the human enzyme, compared to adenosine. In one step selectivity was hence improved over 500-fold.

We would like to thank our colleagues for their numerous contributions to this work. Fred Oppenheimer, Paul Michels, Mike Collins and colleagues in Brussels for providing protein material and carrying out kinetic studies. Fred Velieux, now in Gienoble, and Randy Read, now in Edmonton, for their X-ray studies leading to the three-dimensional structures of GAPDH; and Piet Hereweijn and Ander van Oirschot for the synthesis of the new inhibitors.

05-Molecular Modelling and Design for Proteins and Drugs

Peptides and proteins are attractive targets for designing selective inhibitors which should exhibit high activity for the corresponding enzymes of the human host. The design of selective active site inhibitors is difficult because the active site of an enzyme is usually well conserved in the course of evolution. In contrast, selective inhibition may be easier if the enzyme misses use of a large cofactor. A substantial part of such a cofactor is not directly involved in the catalytic reaction, and as a consequence, its environment is best conserved. We wondered whether the adiponectin portion of NADP would be a good lead for trypanosomal glycerol-phosphate dehydrogenase (GAPDH) and inhibitor design.

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