REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 78 (2010)

From Peptides to Non Peptide Mimetics - A New Generation of Drugs: The Examples of Angiotensin II and Myelin

John Matsoukas

Department of Chemistry, University of Patras, Patras, Greece

SUMMARY

The discovery of Losartan a non peptide Angiotensin II Receptor antagonist was announced in 1989 during the Gordon Research Conference on Angiotensin and the Renin-Angiotensin-System (RAS). The drug was discovered in the Laboratories of Dupont and the announcement at the Conference was the approval for Clinical trials which led to the first Angiotensin II nonpeptide Receptor antagonist. Previous Angiotensin II peptide antagonists such as Sarilesin and Saralasin failed to become drugs due to its peptide nature rendering them susceptible to proteolytic enzymes which hydrolyze them. The announcement was the result of many years work on Angiotensin and the RAS System, since it was discovered 80 years ago. Breakthroughs in this evolution was the discovery of Captopril by Miguel Ondetti in 1975 and Losartan by Timmermans in 1989. In this lecture the main steps followed in our laboratories in Patras are mentioned which led to our Sartan, named Elsartan. Briefly the main steps are: 1. Peptide (The tool), 2. Peptide Model (The ligand – receptor interaction), 3. Cyclic Peptide (The drug lead), 4. Non-peptide mimetic (The Drug).

Immunodominant Epitopes MBP 83-99, PLP 139-151, MOG35-55 of human proteins MBP, PLP, MOG of myelin sheath are implicated in Multiple Sclerosis. These epitopes have been the tools in our laboratories for the Design Synthesis and Preclinical Evaluation in a large number of rationally designed linear and cyclic analogues conjugated to reduced or oxidized mannan via [Lys-Gly] bridge. Specific Analogues have been found to immune rats rendering them potential therapeutics vaccine drugs in the Immunotherapy of Multiple Sclerosis. Furthermore, our cyclic MBP 83-99 peptides, for the first time to be reported as HLA and MHC binders and more stable compared to linear counterparts, possess a series of important immunomodulatory properties rendering them as putative drugs for treating multiple sclerosis and potentially other Th1 – mediated autoimmune diseases. In the light of the results and findings in our research, the main immunodominant peptides MOG35-55, PLP139-151 and MBP83-99 and their head to tail cyclic counterparts conjugated to reduced mannan have been selected to constitute a mixture cocktail drug for preclinical investigation in preparation of New Drug Application (NDA) for Clinical Phase I and II studies in the Immunotherapy of Multiple Sclerosis.