Main Lectures

ML-05.01 STRUCTURE-BASED DRUG DESIGN. By L. N. Johnson, Laboratoire de Moléculaire Biophysique, University of Oxford, Oxford, OX1 3QU, UK.

The earliest known drugs were those derived from natural products whose effects were detected from observation. Such compounds include aspirin, acetylsalicylate, present in the bark of willow (salix) and in the plant meadow sweet (Spiraea alnifolia) from which the name comes and whose organic synthesis was achieved nearly 100 years ago, another example is the antiinflammatory drug, aspirin, from the Chinese herb ging huo (Artemisia annua) whose medicinal use was documented at least 3000 years ago. A later phase of drug design, developed from an intimate coupling of clinical experience and pharmacological modelling, exemplified in the design, screening and treatment of diarrhoeal ulcers. A feature of this work, although much was known of the active agent, histamine, and its physiological effects, nothing was known of the structure of the target molecule, the histamine H2 receptor. The most recent phase in drug design utilizes knowledge of the structures of target proteins or of related macromolecules. Knowledge of the structures of cathepsin D and thermolysin was used in the design of the clinically useful compound cimetidine and, more recently, two potential inhibitors of angiotensin-converting enzyme, the enzyme involved in the regulation of blood pressure. Knowledge of protein structures forms the basis of understanding how a drug can function as a drug in a work with acetylcholinesterase for agents that block neurotransmission, with bacterial DNA gyrase for the action of the quinolone antibiotics, or with HIV reverse transcriptase for the mechanism of AZT. Structural data have led to clues for improvement in properties and explanations of drug resistance as in the crystallographic studies on the binding of anti-HIV compounds to the human rhinovirus, the causative agent of the common cold. Knowledge of enzyme mechanism and specificity led to good mimics of the transition state to provide potential inhibitors as in work with the HIV protease.

Structures of thymidylate synthase, dehydroascorbate reductase and nucleoside phosphorylases have been exploited in the design of agents against cancer. Understanding protein structure has led to new proteins produced by recombinant DNA technology such as a new acting insulin for treatment of diabetes or "humanised" antibodies for the treatment of leukemia and rheumatoid arthritis. Finally new results on the human histocompatibility complex and associated bound peptides and of cytokines and the cytokine receptor complex, or the human growth hormone and its complex with its receptor have provided new insights into basic recognition events in the immune response, the inflammatory response and hormone response, respectively.

The talk will review these achievements of structural biology and describe work from myself and colleagues in Oxford and Aberdeen on the design of new compounds that may be relevant for the treatment of type II diabetes, the non-insulin dependent form of the disease, for which there is no accepted trend for improved drugs. Modern genetic analysis has focussed attention on defects in the enzyme gluconeokinase in the regulation of insulin release in response to glucose and in defects in glycogen synthase in the synthesis of glycogen. In type II diabetes, as a result of diminished insulin release or insulin resistance, there is a decrease in the rate of muscle glycogen synthesis and failure to suppress the uptake of glucose from the liver resulting in elevated blood glucose levels. Regulation of phosphorylation of glycogen synthase and glycosylation breakdown are regulated by mechanisms that involve the reversible phosphorylation of glycogen synthase and glycogen phosphorylase.

Regulation of phosphorylation is also achieved through the inhibitory glycogen. Through knowledge of the detailed structure of glycogen, phosphorylase has been employed in the design, organic synthesis, crystallographic and kinetic analysis of over 50 compounds and has led to compounds with only small modifications from the parent glucosyl that are nearly 100 fold better inhibitors of glycogen phosphorylase. Knowledge of the structures of the target proteins together with advanced computational analysis techniques allows inhibitors to be designed on sound biochemical principles. But it is still a long road to the treatment of patients.

ML-05.01 SYSTEM ATICS OF CRYSTAL PACKING IN MOLECULAR SOULDS. Carolyn Pitts-Brock, Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055, USA.

The ability to predict the structure of molecular crystals, and thus the ability to design molecular crystals, has long been a goal, but the enormous variety of possible structures, as well as the sensitivity of crystal packing to minor molecular modifications, have made the problem appear intractable. The rationalization of structure type possible for simple inorganic salts seemed out of reach.

The availability of large structural databases has changed that situation. Analyses of subsets of structures have begun to reveal principles of molecular aggregation for specific molecular symmetries (e.g., point group 3 and certain intermolecular interactions (e.g., H bonding). Even probabilistic rules are of great value to those seeking to synthesize specific types of molecular solids such as non-linear optical materials (polarization required), or to resolve racemic products by crystallization (chiral space group required).

Phase diagrams are important guides to the synthesis of stoichiometric molecular compounds (i.e., crystals, host-guest complexes, etc.). Such diagrams also illuminate the energy relationships among polymorphs, between solid and liquid states, and between solids and gas. By combining results from semi-empirical atom-atom potential-energy calculations, melting-point determinations, and thermal-motion analyses, free-energy vs. T curves can be estimated and schematic phase diagrams drawn. A major unresolved question is the degree of kinetic control over crystallization. Nucleation is often a very slow process, and surface effects are very important for crystal nuclei.