PREFACE

Compared to the other fields covered by this journal the topics available for this issue encompass a vast array of physiological mechanisms and disorders as well as numerous different classes of pharmacological agents. The precise definition of a 'metabolic agent' is elusive since everything in physiology has a metabolic component and all pharmacological agents affect some physiological process. Thus, distinguishing a metabolic agent from any other agent affecting a physiological system becomes a difficult exercise. Many therapeutically important substances are of endocrine origin or represent modifications of naturally occurring hormonal substances.

This issue of 'Current Pharmaceutical Design' contains the text of eight invited review articles prepared by the leading scientists in their field. The variety of articles submitted illustrates the vast scope of this issue.

The most effective agents, currently available, for lowering high levels of plasma cholesterol are the HMG-CoA reductase inhibitors (HMGRI’s). These agents inhibit the rate determining step in the cholesterol biosynthetic pathway. In his article, Roth describes the genetics of these agents and the attempts, both pre-clinically and clinically, to differentiate them based on their physicochemical properties. Considerable clinical research is ongoing to investigate the anti-atherosclerotic properties of these agents and to determine whether such effects are due to reductions in plasma cholesterol or are the result of 'tissue specific' direct inhibition of cholesterol biosynthesis in cells of the artery wall.

Although widely accepted in clinical practice, there are still concerns about the toxicities observed with the HMGRI’s. Studies suggest that the toxicities of these compounds are mechanism-based and due to a depletion of mevalonate derived products. Biller et al. describe the search for inhibitors of the enzyme squalene synthase using three of the major methods for drug discovery: rational design, synthetic chemical screening and natural products screening. Inhibitors of this enzyme have several potential advantages over HMGRI’s. This enzyme is located at the final branch point in the cholesterol biosynthetic pathway and is the first step committed to the synthesis of sterols. Selective inhibitors of this enzyme are expected to block cholesterol biosynthesis, without having deleterious effects on the branch pathways of isoprene biosynthesis.

In his article, Schroefer describes the rational design of improved oxysterols for the treatment of hypercholesterolemia. These agents inhibit sterol biosynthesis and suppress the levels of HMG-CoA reductase (HMG) activity. The mechanisms by which these agents suppress HMG activity is an area of intense investigation since they have little effect on HMG activity and several studies have shown that these compounds lower enzyme activity by primarily inhibiting gene transcription and/or accelerating the degradation of the enzyme.

Atherosclerosis is initiated or aggravated by a variety of risk factors, such as elevated cholesterol levels, obesity, hypertension, smoking, diabetes mellitus or personality traits. Most of the established risk factors are controllable by various methods, however, there is a strong genetic component to the development of atherosclerosis which to date has been unmanageable. The identification of this genetic component has been the subject of intense research for decades.

In their review, Koschinsky and Ramharack describe the structure, function and regulation of a genetically determined lipoprotein particle, lipoprotein (a). Elevated levels of this lipoprotein are associated, both qualitatively and quantitatively, with an increased risk of coronary heart disease and stroke. The mechanism of the pathogenicity of Lp(a) is still under investigation, however a number of mechanisms have been postulated and they fall broadly into two groups: delivery of lipids to atherosclerotic lesions and modulation of thrombosis and fibrinolysis. To date, efforts to lower the levels of this lipoprotein, either through dietary or pharmacological methods, have been disappointing.

Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease affecting approximately 5% of all the adults in the United States. The long term complications of this disease include cardiovascular disease, retinopathy, neuropathy and nephropathy. Recent clinical trials have shown that improving glycemic control in these patients can significantly reduce these complications. Current therapies depend mainly on the administration of insulin secretagogues such as the sulfonylureas and biguanides, however, these therapies can produce life-threatening episodes of hypoglycemia. Hulin et al. describe the development of a new class of antidiabetic agents, the glitazones, which lower plasma glucose levels without an increase in insulin release. Studies have revealed effects on gluconeogenesis, glucose transport and glucose transporter expression.

Dihydrotestosterone, a product of 5α-reduction of testosterone, has been implicated in the pathology of benign prostatic hyperplasia (BPH), acne and male pattern baldness. Progress in the development of potent isozyme selective and dual inhibitors of 5a-reductase is reviewed by Frye with an emphasis on structure activity...
relationships as well as the results of human clinical studies with finasteride, a 5α-reductase inhibitor recently approved by the FDA for the treatment of BPH.

Williams and Pettibone describe the significant progress made in the design and discovery of new classes of oxytocin antagonists (OA's). Continued study of various OA's has resulted in the identification of smaller peptidic antagonists as well as several classes of non-peptidic OA's. Human clinical studies with the peptidic OA, atosiban, have implicated oxytocin in the pathophysiology of preterm labor and suggests that the administration of an OA may provide a new method for preventing premature birth.

Hormones and other ligands for nuclear receptors have a vast array of biological effects and many human diseases occur as a result of abnormal production or utilization of hormones or as a result of inherited conditions in which nuclear hormones are altered. In their review, Jones and Petkovich discuss the steroid/thyroid hormone receptor superfamily, and how knowledge of receptor structures and mechanism of action may be exploited therapeutically to alter their effects on gene expression in human disease states.

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