PHARMACOGENETICS FROM MOLECULAR TO CLINICAL

Hong-Hao Zhou

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Hong-Hao Zhou

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内 容 提 要

本书是作者近 20 年的研究论文集。包括药物代谢和反应的种族差异、药物代谢酶遗传多态性、药物受体遗传多态性、环境和遗传因素在药物代谢酶功能调节中的相互作用等七个部分。所有论文均发表在 SCI 收录的国际权威杂志如新英格兰医学杂志上，反映了作者创建的具有国家和民族特色的遗传药理学理论体系。本书适合于生命科学领域的专业人员，尤其是从事遗传药理学、药物基因组学、药理学和临床医学的教学、科研和临床工作的专业人员。

This book is a collection of the author's research papers in the area of pharmacogenetics published in current 20 years. It covers seven parts including ethnic differences in drug metabolism and responsiveness, genetic polymorphisms of drug metabolizing enzymes, genetic polymorphisms of receptors, interactive effect of environmental and genetic factors on drug-metabolizing enzymes, etc. All papers in this collection were published in prestigious peer-reviewed journals including New England Journal of Medicine and were cited widely by many articles and books. These papers reflect the author's pharmacogenetics theory as a system with distinctive features of his own state and nation. This book is particular for the specialists in life science especially pharmacogenetics, pharmacogenomics, pharmacology and clinical medicine.

主编简介

周宏灏，男，汉族，1939.5.29出生于湖南长沙。1962年毕业于武汉医学院医疗系。现为中南大学国家重点学科药理学首席教授，并任临床药理研究所所长、药品临床研究国家培训中心主任、临床药理国家培训中心主任，美国默沙东(Merck)国际临床药理奖学金评委国际药理学联合会(IUPHAR)遗传药理学和药物基因组学学会创始成员(Founding Member)、国际药理学联合会药物代谢学会理事(Councilor)、中国药理学会常务理事、中国药物代谢专业委员会主任委员、湖南省药学会理事长、湖南省临床药理专业委员会主任委员，《Br J Clin Pharmacol》、《Current Pharmacogenomics》、《Asian J Drug Metab & Pharmacokin》、《Acta Pharmacol Sin》、《中华医学杂志》等10余家杂志编委。历任湖南医科大学药理教研室主任、遗传药理学研究所所长、基础与临床药理研究所所长、湖南医科大学副校长并兼任湖南省药品监督管理局副局长（顾问）。

周宏灏教授自20世纪80年代初起始终围绕药物反应个体差异和种族差异及其遗传机制进行了系统、深入的研究，并取得了一系列令人瞩目的研究成果。1985年至1991年在美国Vanderbilt大学研究证实了药物反应种族差异，并深入阐明了产生机制，研究结果在《N Engl J Med》发表后，在国际医药学界产生重要影响。1991年他从美国回国后，连续获得两项国家自然科学基金重点项目和三项美国中华医学基金会项目资助，创建了我国第一所遗传药理学研究所，在国内首次为研究生开设了遗传药理学课程，主编和出版了我国第一部《遗传药理学》研究生教材和《遗传药理学》专著，培养了90余名硕士和博士及博士后，造就了一支遗传药理学研究队伍。他是我国遗传药理学科的开拓者和带头人，在国际药学及药理学界享有较高声誉。先后20余次被国际学术会议邀请作大会专题报告或会议主席，并被美国、加拿大、日本、韩国和香港等国家和地区十多家大学邀请作专题学术报告。他和他领导的研究队伍的工作使我国遗传药理学和临床药理学研究处于世界先进水平。

Biographical notes for Professor Hong-Hao Zhou

Professor Hong-Hao Zhou was born and brought up in Changsha, Hunan, China. He proceeded to study medicine at the Wuhan Medical School in 1957. He had a distinguished undergraduate record and graduated in 1962. After serving 16 years as a physician, he moved to Changsha in 1978 and worked at the Hunan Medical University as a Lecturer, Associate Professor and Professor in pharmacology and clinical pharmacology from then till now. He is currently the Chair Professor of Pharmacology and the Chairman of Institute of Clinical Pharmacology and the Director of Pharmacogenetics Research Institute at Central South University. He founded the unique Pharmacogenetics Research Institute in China.

His major research interests are ethnic differences in drug metabolism and response, genetic polymorphisms of Drug-metabolizing enzymes and receptors, the interactive effects of genetic and environmental factors on drug metabolism. He published extensively on pharmacogenetics and clinical pharmacology and was one of the first scientists to explore the evidence and mechanism of ethnic differences in drug response. He also did extensive work on the genetic polymorphism of drug-metabolizing enzymes and receptors. This work brought him a number of prizes and grants as well as international reputation.

Professor Zhou has served as the President of the Society for the Drug Metabolism and Pharmacokinetics of China. He has served for IUPHAR as a Councilor on the Drug Metabolism Section and a Founding Member on the Pharmacogenetics and Pharmacogenomics Section. He joined the Selection Committee for Merck Sharpe & Dohme International Fellowships in Clinical Pharmacology since 1998.

He is a member of editorial board for British Journal of Clinical Pharmacology, the Journal of Current Pharmacogenomics, Asian Journal of Drug Metabolism and Pharmacokinetics. He reviewed numerous manuscripts for peer-reviewed journals including New England Journal of Medioine, Circulation, Journal of Pharmacology and Experimental Therapeutics and Clinical Pharmacokinetics.

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Preface

Response to drugs shows significant inter-individual variations and ethnic differences. The biological (age, gender, disease and genetics), cultural and environmental factors contribute to these variations. The most important aspect is the genetic variability between individuals in their ability to metabolize drugs due to expression of polymorphic enzymes. The clinical value of understanding pharmacogenetics is in its use to optimize therapeutic efficacy, prevent toxicity of those drugs whose metabolism is catalyzed by polymorphic isoenzymes, and to contribute to the rational design of new drugs.

This book is a collection of author's research papers in the area of pharmacogenetics published in current 20 years, which reflects the development course of pharmacogenetics as a new area in life science. Each chapter in this book is an individual research report and contributes a piece in the field of pharmacogenetics. It covers seven parts, including ethnic differences in drug metabolism and responsiveness, genetic polymorphisms of drug metabolizing enzymes, genetic polymorphisms of receptors, interactive effect of environmental and genetic factors on drug-metabolizing enzymes, etc. All papers in this collection were published in prestigious peer-reviewed journals including New England Journal of Medicine and were cited widely by many articles and books. These papers reflect the author's pharmacogenetics theory as a system with distinctive features of his own state and nation. This book is for specialists in life science especially pharmacogenetics, pharmacogenomics, pharmacology and clinical medicine.

I acknowledge the exceptional role of Professor Kumana CR, MD from University Department of Medicine, Queen Mary Hospital, Hong Kong University, in bringing me into the field of clinical pharmacology, of which pharmacogenetics is a new frontier. I am very fortunate to have worked with Alastair J. Wood and Grant R. Wilkinson at Vanderbilt University whose enthusiasm, expertise, and dedication greatly contributed to my Career and the production of this book. I am grateful to all contributors of this book for their hard work in conducting the studies and in writing the chapters. I acknowledge the editorial support of Mrs. Dan Wang and Mr Yuan-Fei Huang and the staff of Institute of Clinical Pharmacology, Central South University, for their consistent and ongoing support.

Changsha, May 29, 2003

Hong-Hao Zhou

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Part 1

Ethnic Differences in Drug Metabolism and Responsiveness

Racial Differences in Drug Response: Altered Sensitivity to and Clearance of Propranolol in Men of Chinese Descent as Compared with American Whites

Hong-Hao Zhou, Richard P Koshakji, David J Silberstein, Grant R Wilkinson and Alastair JJ Wood

ABSTRACT

To determine whether the pharmacokinetics and pharmacodynamics of beta-blockade differ among racial groups, we gave 10 men of Chinese descent and 10 American white men 10, 20, 40, and 80 mg of propranolol every eight hours; the dosages were given in random order, and each dose was given for one day. The degree of beta-blockade was measured as the reduction in the heart rate and blood pressure in the supine and upright positions and during treadmill exercise testing.

The Chinese subjects had at least a twofold greater sensitivity to the beta-blocking effects of propranolol than the white subjects, as indicated by the mean (±SEM) plasma concentrations producing a 20 percent reduction in the heart rate in both the supine position (197 ± 31 *vs* 536 ± 58 nmol per liter; $P<0.05$) and the upright position (131 ± 27 *vs* 343 ± 39 nmol per liter; $P<0.05$) and after exercise testing (96 ± 12 *vs* 185 ± 23 nmol per liter; $P<0.05$). In addition, the Chinese subjects had much greater sensitivity to the hypotensive effects of propranolol, as shown by the concentrations that reduced blood pressure by 10 percent in the supine position (73 ± 5 *vs* 748 ± 7 nmol per liter; $P<0.01$) and in the upright position (89 ± 5 *vs* 401 ± 6 nmol per liter; $P<0.01$). No difference in beta-receptor density or affinity of lymphocytes was found between the groups. The Chinese group had a 45 percent higher free fraction of propranolol in plasma, which may have contributed to the increased drug effect but cannot explain it entirely. This group metabolized propranolol more rapidly than the white group, which resulted in a 76 percent higher clearance of an oral dose (3740 ± 737 *vs* 2125 ± 214 mL per minute; $P<0.05$) because of increased metabolism through multiple metabolic pathways.

We conclude that Chinese men have greater sensitivity than white men to the effects of propranolol on heart rate and blood pressure. Decreased protein binding may be responsible in part, but most of the effect remains to be explained.

INTRODUCTION

Much of the knowledge used to design therapeutic regimens has been gained in only one or two ethnic groups. Many studies of drug effects in humans do not describe the ethnic or racial backgrounds of their subjects, and of those that do the majority have included only whites and American blacks. In spite of this limitation, the findings derived from these studies are often applied to other ethnic or racial groups.

The importance of genetic factors in controlling the disposition of drugs has recently received increased attention. It has been recognized for some time that the capacity for *N*-acetylation of various drugs is genetically determined and that the proportions of persons with fast acetylation and of those with slow acetylation vary among populations.(Lunde et al., 1977; Clark 1985; Horai et al., 1988) More recently, genetic differences in drug

oxidation have been defined, especially in the ability to oxidize debrisoquin and sparteine; about 8 to 10 percent of the American population and 0.7 percent of the native Chinese population poorly metabolize debrisoquin and a number of other drugs, including propranolol, which are also metabolized by the same cytochrome P-450 isozyme.(Inaba et al., 1985; Otton et al., 1984; Jacqz et al., 1986; Lou et al., 1987)

The dosage of propranolol prescribed in China is substantially lower than that widely used in the United States and Europe, because of a perception that Chinese patients respond to lower doses. If such a perception is correct, the different responsiveness of Chinese patients to propranolol may be due to either a difference in the disposition of the drug, resulting in higher drug concentrations in plasma, or a difference in drug sensitivity, inducing a change in responsiveness to similar drug concentrations.

The aim of this study was to investigate the relative contribution of pharmacokinetic and pharmacodynamic factors and to determine whether changes in cardiac sensitivity could be explained by changes at the beta-receptor itself, with lymphocytes used as a model.

METHODS

Ten men of Chinese descent and 10 white men gave written consent to participate in this study, which was approved by the Vanderbilt University Committee for the Protection of Human Subjects. None of the subjects had any abnormal finding on routine laboratory tests, history taking, physical examination, or electrocardiography. All subjects were nonsmokers and had not taken medication or drunk alcohol for at least two weeks before the study. The mean age of the Chinese subjects was 27 ± 8 years (range, 20 to 40), and that of the white subjects was 28 ± 6 (range, 19 to 44). The mean weight of the Chinese subjects was 64.7 ± 9.5 kg (53 to 81), and that of the white subjects was 77.4 ± 7.3 kg (67 to 90). All Chinese subjects were of Chinese descent only; six had been born in the People's Republic of China, three in Taiwan, and one in Indonesia of Chinese parents. The Chinese subjects had spent six months to three years in the United States (mean, 1.6 years), and all had primarily Western diets. All white subjects had been born in the United States. Since the debrisoquin polymorphism (Raghuram et al., 1984) has been shown to affect the disposition of propranolol, the phenotype was determined in each subject according to standard techniques. (Jacqz et al., 1986)

Each subject underwent treatment for one day with each of four dosages of propranolol — i.e., 10, 20, 40, or 80 mg every eight hours. The order of administration was randomized according to a table of random numbers. The blood pressure (the mean of two measurements obtained by the same observer with the same mercury sphygmomanometer) and heart rate were measured by electrocardiography, with the subject in both the supine and upright positions, four hours after the last dose of propranolol at each dosage level had been given. At the same time a blood sample was obtained for measurement of the propranolol concentration. The heart rate was also determined by electrocardiography during the last 15 seconds of 5 minutes of treadmill exercise (1 minute at 1.7 miles per hour [2.7 km per hour] at 10 percent grade, 1 minute at 2.5 mph [4 kph] at 12 percent, 1 minute at 3.4 mph [5.4 kph] at 14 percent, and 2 minutes at 4.5 mph [7.2 kph] at 16 percent). The workload was determined as that necessary to increase the heart rate to 150 beats per minute without beta-blockade. The extent of beta-adrenoceptor blockade was expressed as the percentage reduction in heart rate during the last 15 seconds of exercise, as compared with the baseline values.

Blood samples (50 mL) were drawn from each subject before the study and before propranolol administration. Lymphocytes were isolated immediately for measurement of beta-adrenoceptor density and affinity by saturation analysis (Feldman et al., 1984) with use of the radioligand [^{125}I] iodopindolol. Lymphocyte membranes were prepared according to a modification of a method previously described. (Feldman et al., 1983)