Psychopharmacogenetics
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FOREWORD

Michel HAMON, and Philip GORWOOD

Considerable progress has been made for the last fifty years in the treatment of psychiatric disorders thanks to the empirical discovery of the psychotrophic properties of a few drugs. Actually, antipsychotics first, then antidepressants, anxiolytics and mood stabilising agents have all been discovered at the beginning of the second half of the last century, causing a true revolution in the clinical practice of psychiatrists, and the definitive recognition of psychiatry as an actual clinical discipline, with the use of effective drugs in addition to other medical interventions, as for cardiology, internal medicine, etc.

However, serious limitations in this progress have been the relatively low proportions of patients responding to the drugs, the unpredictability of the response, and the deleterious side effects of the first antipsychotics and antidepressants which sometimes considerably deteriorate the quality of life of patients, and explain the poor compliance to treatments. A second breakthrough in the clinical practice of psychiatrists has then been achieved from the seventies, i.e. 30 years ago, when novel drugs were developed on the basis of the extensive neuropharmacological investigations that followed the empirical discovery of the first psychotrophic drugs. Indeed, because clear-cut data showed that tricyclic antidepressants act through the blockade of monoamine reuptake, chemists synthesized selective monoamine uptake inhibitors which then revealed to share with tricyclics potent antidepressive properties. Similarly, the demonstration that phenothiazine and butyrophenone antipsychotics actually act through the blockade of dopamine receptors led to the development of selective dopamine receptor antagonists, such as the benzamide compounds sulpiride and amisulpride, which are endowed with clear-cut antipsychotic properties. Such achievement was a clear breakthrough because these novel drugs, specifically designed to act selectively at clinically relevant molecular targets, are consequently endowed with much less secondary, deleterious, effects of the first psychotropes. Indeed, the quality of life of patients treated with this second generation drugs is markedly improved compared to that degraded by earlier drugs, which contributes to higher compliance, and, in turn, better efficacy. However, better does not mean optimum because a large proportion of

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depressed or psychotic patients still do not respond to these second generation drugs. Indeed, at least 30% of depressed patients are not responsive to potent antidepressants, but the reasons why they do not respond are not known.

A third step in the development of better treatments is therefore needed, and neuroscientists and clinicians are strongly determined to make it fully successful. This step actually involves two complementary approaches. The first one consists of improving the design and synthesis of pharmacologically active molecules in order to increase the effectiveness and safety of drugs aimed at alleviating psychiatric disorders. Chemists already produced multi-target drugs acting at several receptors, enzymes, transporters, relevant to these diseases, but still (mostly) devoid of undesirable side effects. These third generation drugs (such as atypical antipsychotics acting at both dopamine and serotonin receptors, or anti-depressants acting simultaneously at serotonin reuptake site and presynaptic auto- or hetero-receptors) are clearly a further progress toward better treatments. However, even much more can be expected from the second approach of this third step, which consists of considering the genotype as a possible reason for good, poor or no responding to drugs. This field of research is the domain of Psychopharmacogenetics.

The objective of this book is to present all aspects of this novel discipline which aims at identifying the possible genetic reasons causing a given patient to respond, or not respond, to a psychotropic drug, and to suffer, or not suffer, from side effects caused by this drug. For this purpose, we asked the best experts in the world to contribute to this enterprise, and all accepted with great enthusiasm. We are very grateful to all of them, for their remarkable and comprehensive contributions. The book is organized in three main parts. The first one, with the first 9 chapters, is devoted to the various major psychiatric disorders for which one can expect so much from Psychopharmacogenetics, as definition of patient’s genotype should be of great help to design the best drug treatment specifically for this patient, with maximal chance of positive response and minimal risk of side effects. For instance, polymorphism in the promoter region of the gene coding the transporter responsible for serotonin reuptake seems to be critical in the response to second generation antidepressants. The second part aims at providing detailed knowledge on major molecular targets of psychotropic drugs, with particular focus on polymorphisms of relevant genes which play key roles in both the neurobiological mechanisms underlying the diseases and the mechanisms of actions of these drugs. In the last part of the book, possible genetic reasons accounting for side effects of psychotropic drugs are reviewed, concerning cardiac, motor and sexual functions, notably because of marked individual differences in the metabolism of drugs.

Clearly, drug treatment of psychiatric disease is a real challenge, and also a bet as it is extremely difficult to predict the quality of individual response. Psychopharmacogenetics is undoubtedly a potent approach toward better treatment by identifying responders based on genotype profile. We do hope this book will contribute to open this novel discipline in the field of psychiatry, and to promote a novel method of great potential for the design of more effective and surer treatment adapted to a given patient.
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