Pharmacology and Biochemistry of Psychiatric Disorders

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Preface

It is apparent that there is no book which is suitable for recommending to undergraduate and graduate students studying central nervous system pharmacology or to psychiatrists and others studying biochemical and pharmacological aspects of psychiatric disorders. Instead a long reading list of publications is required which fails to provide an overall perspective.

There are several excellent books dealing with either more basic aspects of neuropharmacology (particularly Cooper, Bloom and Roth, 1978) or therapeutic aspects of neuropharmacology (e.g. Barchas *et al.*, 1977). The aim of this book is to provide an overview of the current state of knowledge of the pharmacology and biochemistry of psychiatric disorders in a form accessible to readers approaching the subject from different disciplines. We have therefore examined the experimental pharmacological data on drugs used in psychiatry and discussed whether they can be linked with clinical and biochemical findings. We have avoided trying to 'make a story' in order to reach a satisfying conclusion but rather reviewed the major information: it is still possible to present information to support the notion that there is decreased monoamine function in depression; however, current experimental data do not support the idea very strongly. We have therefore presented the results that seem to be important. Readers having been given some of the historical data and more recent research will then, we hope, be in a better position to evaluate the current research.

However, we have included two chapters that do not directly reflect these aims. The first is a chapter on the basic biochemistry of neurotransmitters as some knowledge is necessary for understanding both the pharmacology and the clinical biochemistry. The second is a chapter on Parkinson's disease, which is included because it serves as a paradigm for a condition caused by abnormalities in a brain neurotransmitter system, and where the pharmacological treatment has developed from biochemical studies.

The sections on clinical aspects have been included for two reasons. They allow workers with little clinical experience (pharmacologists, experimental psychologists, or preclinical students) to get some 'feel' for the disorder for which the drugs are given. They also allow us to point to problems associated with clinical neuropharmacological research. These sections are not intended to be comprehensive and in some cases are oversimplified for the sake of clarity, although not to the point of being misleading. For those wishing to pursue clinical aspects further, modern texts have been published in the United States (Freedman, Kaplan and Sadock, 1980), and by workers at the Institute of Psychiatry (Hill, Murray and Thorley, 1979). There will shortly also be one from the University of Oxford (Gelder, Gath and Mayou, 1982).

Not all the clinical sections follow the same format, as the aetiology, pathology, and treatment of different disorders may be concerned to different extents with the pharmacology. We have nevertheless tried to maintain as much uniformity as possible.

Papers have been cited for three reasons: that they are major papers (perhaps for historical reasons), that they are good reviews, or that they report work too recent to have been fully reviewed elsewhere. This system may be unfair to some workers in that it fails to give them credit for important work, but it prevents the reference list becoming unwieldy.

We have included several appendices, in an attempt to provide easy access to some basic facts. The glossary provides a dictionary of specialist terminology which may be encountered in this and other publications.

Not surprisingly, the book reflects our own views, and indeed prejudices, on current important areas of research. In a few years some sections will be out of date. We hope that this will reflect advances in knowledge rather than a failure on our part to identify important trends.

We thank the various publishers and authors who have generously allowed us to reproduce data from their publications. It is a pleasure also to thank Fiona Teddy for her typing of the manuscript. Finally we should like to acknowledge the invaluable comments of many of our colleagues, particularly Dr Philip J. Cowen and Dr David J. Nutt. We have not always followed their advice and remaining errors are the responsibility of the authors.

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Chapter 1

Introduction – Strategies in Psychopharmacology Research

1.1 The problems of psychiatric assessment

A major problem for research in psychiatry, and particularly for psychopharmacological research, is that of accurate diagnosis; that is the delineation of specific conditions or illnesses. The problem of classification is a continuing one for psychiatry, and new systems are regularly introduced as offering advances over existing ones. Although most psychiatrists are agreed on the typical characteristics of schizophrenia, depression, and other disorders, devising a classification which meets even the very basic requirements of having categories which are mutually exclusive and jointly exhaustive has proved elusive, atypical cases being difficult to categorise. When one also includes the requirement that a classification should provide implications for both treatment and outcome, the position becomes fraught with difficulties.

Much of the research and controversy in psychiatry has been concerned with this exact clinical delineation (see Section 3.4) and whilst there has been some validation of the distinction between the major illnesses by differential responses to treatment, subdivisions of these illnesses and the placing of atypical cases, have been less successful.

Such difficulties have led some people to question the validity of the concept of psychiatric illness. There is insufficient space here to do justice to arguments which could easily fill the whole of this book, but it is not to avoid the issue to suggest that an open mind should be kept on the concept of illness, whilst arguing that a consideration of patterns of distress, and ways of relieving it, is a justifiable goal.

Study of the development of medical classifications of illness shows a change in the basis of the systems. Initially classified on signs and symptoms, as knowledge progresses this system is replaced by a classification based on pathology (usually derived from investigating groups identified on the basis of physical signs) and finally by a system which considers aetiology. This last is the ultimate aim for nosologists, and does not necessarily require a knowledge of specific pathology, as it may be inferred from epidemiological data.

With a few exceptions in the field of mental subnormality, psychiatric illnesses are recognized and classified solely on the basis of symptoms and signs. Unlike

many (but not all) physical illnesses there is no objective biochemical or physiological test which can be used to confirm or validate any diagnosis, give any indication of appropriate treatment, or help to predict outcome.

Why is this thought to be a reasonable goal, and why has so much effort been expended on the search for neurochemical changes in psychiatric illness? One answer to the first question is that historically, conditions which were included with psychiatric illness were found to have an organic basis when appropriate technology became available. The prime example of this is General Paralysis of the Insane, caused by the spirochaete of syphilis, but others include some cranial tumours, and metabolic disorders. More rational forms of treatment were then introduced. In answer to the second question it is now known that a variety of hormonal and metabolic disturbances, either 'spontaneous' or drug induced, produce symptoms indistinguishable from psychiatric disorders, and that the drugs effective in treating psychiatric illness have marked actions on central neurotransmitter systems, suggesting that some biological process may be associated with the clinical symptoms. This line of thought, however, leads to an assumption generally made, that more specific delineation of clinical symptomatology improves the likelihood of finding a biochemical marker of pathology.

This is of course justifiable only where there is a one to one relationship between clinical symptoms and aetiology; that is to say that there is a pattern to the symptoms and signs produced by any causal factor, and that these are specific to it. The paradigm of this is infective illness. This is unlikely to be the case in psychiatry since there is evidence that aetiology of the major illnesses is multifactorial, that many symptoms occur in different disorders and single disorders have a wide variety of presentations of symptoms.

That this approach should have produced results in the past is evidence only that *some* conditions have such a one to one relationship, and were therefore selectively identified. It may be that the residual 'pool' of illness has much more complicated aetiological relationships.

Although some of the classificatory systems are described as multifactorial in that they include factors other than clinical symptoms and signs (e.g. duration, physical illness, social functioning, past history, family history), most combine all these factors in a single diagnostic schedule, thereby confusing the contributions of the various factors in the aetiology. An exception is the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (DSM-III) (Task Force, 1980) which defines five separate axes, but which nevertheless fails to provide separate evaluations of past history, family history, or specific social factors.

The important point for research, however, remains that diagnoses made should be reliable and generally agreed as valid. Both the research diagnostic criteria of Spitzer *et al.* (1975) (which has influenced the DSM-III) and the Present State Examination (PSE) with computerized CATEGO diagnosis of Wing, Cooper and Sartorius (1974; see Section 5.5) meet these criteria and are widely used.

A further problem is that of rating psychiatric illness. This is discussed in the

appropriate sections but there are some general points.

The function of these scales is quite distinct from diagnosis. The scales are tools to assess the severity of particular diagnoses and they should measure reliably what they are intended to measure. This is usually assessed when the scales are introduced, by comparison with a general clinical assessment, or with pre-existing scales. It is important to note, however, that they are usually assessed in specific clinical settings, (e.g. depressed inpatients) and findings may not generalize to different patient groups.

Their purpose is generally to allow one to assess change, usually improvement. It is therefore important that they should be reliable. Test–retest reliability is, however, difficult to assess in practice, as patients either get used to answering the test in a particular fashion (the 'halo' effect) or their symptoms change. Computerized statistical analyses to allow for these factors are available, but are rarely employed. Scales should furthermore be reliable when used by different raters – inter-rater reliability. This is easier to assess and may be done in a variety of ways.

For these reasons most confidence is placed in established scales with extensive background data available. However, improvements are suggested often to facilitate administration, e.g. by patient self-rating, but also to improve their value, for instance by being more sensitive to change. It is important that such scales should receive general validation to ensure that they are not improving their apparent sensitivity at the expense of validity, for instance that response to treatment by a particular group of drugs reflects true improvement, and not solely the non-therapeutic changes induced by drug treatment.

1.2 The problems of investigating clinical biochemical changes

The problems of investigating biochemical changes in the brain during psychiatric disease are formidable and can most simply be stated as follows:

Where to measure?
What to measure?
What do the results obtained mean?

These will be dealt with in turn but are clearly inter-related to some extent.

Where to measure? In general it is impossible to measure biochemical changes occurring in the brain. The only exceptions occur during neurosurgery, an uncommon event during psychiatric illness, or by analysis of post-mortem brain.

Studies on post-mortem brain have been valuable, particularly in Alzheimer's disease (Chapter 6), Huntington's chorea (Chapter 7), Parkinson's disease (Chapter 8), and to a lesser extent schizophrenia (Chapter 5). Nevertheless there are still major problems. Many neurotransmitter concentrations and enzyme activities change rapidly after death. Immediate freezing of tissue after death is invariably impossible for social, ethical, legal, and practical reasons. The cause of death can influence results; for example, oxygen deficit altering enzyme activity, because the subject died from bronchopneumonia. Finally patients in those countries where most research is carried out will almost certainly have been on

drug therapy. Most drugs will influence and perhaps 'mask' pathological biochemical changes. This applies not only to transmitters and enzymes but also to receptor systems.

Clearly we would like, where possible, to have relatively non-invasive methods of study, whereby the patient can be studied when ill and, at least in those psychiatric conditions such as acute schizophrenia, depression, and mania, following remission of symptoms.

Cerebrospinal fluid concentrations of transmitters and metabolites have been studied, but the procedure of lumbar puncture is not without risk. There is also now the question as to whether CSF neurotransmitter metabolite concentration always reflects metabolic changes in the brain. Even if they do there is little evidence to suggest that metabolism and function are always closely related.

Blood and urine are usually simple to collect, although even this can be a problem, especially in very ill patients and outpatients. However, the general feeling now is that little data of value can be gained by examining transmitter precursors and metabolites in either fluid because of the small fraction of total product that is either required or alternatively produced by the brain.

Following the introduction of ligand–receptor binding techniques for studying receptor populations (Section 2.14) there has been effort expended to see whether there are changes in peripheral receptors which may reflect changes in receptor function in the brain. Some useful data on α-adrenoceptors and 5-HT receptors on platelets are now appearing, but the major assumption has to be made that any change reflects a central change.

What to measure? The obvious answer to this is that one measures what one has the technology to measure! However, the clear corollary of this does not always seem to be realized. One cannot measure compounds for which we do not have the methodology or those compounds which have not been identified (many probably exist). If we estimate the total number of synapses in the brain and calculate the concentration of the known transmitters necessary for these terminals, we can account for only a small proportion (say 10–20%).

We measure what we can, but there is no technology available that allows one to 'explore' for new compounds. In practice what is done is to make an educated guess that compound 'X' may be in the brain, develop the methods to identify it and then extract brain tissue to see if it is present. This has happened with the peptides (Chapter 2, Part 5) and accounts for the explosive growth in the number now known to be present in the brain.

In general the compounds measured have been the neurotransmitters and their metabolites in brain or peripheral tissues; their synthetic and degradative enzymes in the brain and occasionally peripherally (such as platelet monoamine oxidase activity). Such measurements will indicate major metabolic changes, but do not necessarily indicate dynamic changes (i.e. synthesis rates) or functional changes which may not be closely linked to metabolic changes. After all, presumably what we are interested in is the function of the 'system', how much transmitter is available to stimulate the receptor, and whether on stimulation there is a change in response.

In an attempt to answer this last point various studies have now employed ligand–receptor binding techniques to examine whether receptors have been altered. Again this has been performed mainly on post-mortem brain tissue, but also occasionally on platelets and leucocytes, now it is known that they have 5-HT, dopamine, or α-receptors on their membranes. Assumptions then have to be made as to whether any peripherally measured change reflects a central change.

Other recent attempts to examine receptor function have included the use of 'challenge' tests, particularly neuroendocrine tests. Growth hormone release is under dopaminergic and adrenergic control; prolactin release inhibitory factor is probably dopamine. The technique therefore is to challenge these systems with agonists or antagonists to see if the response is abnormal in pathological states, the reasoning being that in illness there might be a general up- or down-regulation of the receptors, not only in various brain areas, but in the hypothalmic–pituitary systems as well. Such approaches are still in their infancy and hampered by the complexity of the mechanisms involved in controlling neuroendocrine release; mechanisms which are still being elucidated.

What does it mean? Lastly we come to interpretation of data. One must make sure that any differences observed have not resulted from some of the problems outlined above – drug treatment, age or sex of patient (proper control selection is always vital), storage of tissue, etc. What will still not be known is whether the observed change has any primary relationship to the disease process or whether it is secondary – that is whether the change caused the disease or whether it has occurred because of alterations in other neurotransmitter systems and has little bearing on the aetiology or pathology of the disease process. To try to answer that is a formidable problem and we often therefore use pharmacological data as a further clue.

1.3 The problems of investigating the pharmacology of psychoactive drugs

In some ways the problems of investigating the pharmacology of psychiatric illness are those associated with examining the clinical biochemical changes 'where to measure?'; 'what to measure?; and what does it mean?'. The main advantage of pharmacological research is that we can use experimental animals, but of course, that gives rise to its own problems.

If animals are given psychoactive drugs, they can be killed and changes looked for in all tissues including brain. Nevertheless there are problems in deciding the optimum dose (most doses in animals are not comparable on a dose/weight ratio to those in humans) and there can be marked species differences. Furthermore it is often important to give the drugs chronically. Both tricyclic antidepressants and ECT work to alleviate depression only when given over a period of time. Much of the earlier work on the changes produced by single doses of tricyclic or a single electroconvulsive shock has told us little about their therapeutic mechanism of action and may have been frankly misleading.

Furthermore we do not believe there is any totally satisfactory animal model of psychiatric disorder. Drugs cannot therefore be given to a 'pathological' brain to