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Psychopharmacology Recent Advances and Future Prospects

EDITED BY

Susan D. Iversen

Psychopharmacology:
Recent Advances and Future Prospects

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Psychopharmacology: Recent Advances and Future Prospects

BRITISH ASSOCIATION
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Preface

The tenth anniversary of the British Association of Psychopharmacology was celebrated in Guernsey on 4–7 April 1984. It was decided that the occasion should be marked by a meeting that was special both in venue and in scientific content. Psychopharmacology as a discipline continues its rapid growth drawing scientists from many disciplines in their quest to unravel the mode of action of drugs on brain function both in health and disease.

We elected to undertake a broad review of the whole subject, in the belief that so many advances have been made in the past few years that it should be possible to devise a stimulating meeting and useful reference volume to mark our tenth anniversary.

Five topics were selected for review, and these illustrate well the state of the art and focus on a number of fundamental issues in psychopharmacology.

The President, Gene Paykel organized a review of current research on antidepressants. A wide range of effective antidepressants exist, most of which inhibit the re-uptake of noradrenaline or serotonin in brain. Dr Pinder reminded us that more than 150 compounds, mainly using these mechanisms are in various stages of development by the pharmaceutical companies. A few atypical antidepressants of uncertain neuropharmacological mechanisms are available, but major breakthroughs in the treatment of depression seem unlikely until more is known of the aetiology and neuropharmacological basis of the disorder. Clinicians repeat that anti-depressant drugs with a more rapid onset of action than existing agents would be valuable. It is notable that there are few animal tests modelling the behavioural features of depression which respond reliably and selectively to antidepressant drugs. However, in view of the slow onset of action of these drugs, it is surprising that behavioural pharmacologists rarely study chronic dosage regimes in animals.

Turning to the second topic, the minor tranquillizers, the major breakthrough afforded by the discovery of the endogenous benzodiazepine receptor can begin to be appreciated. When specific receptors for a class of drug molecules can be described and studied, rapid advances can be made in medicinal chemistry to design novel ligands. In the case of the benzodiazepines this approach had led both to the discovery of a range of non-benzodiazepine agonist ligands and the introduction of a novel pharmacological concept – that of the 'inverse agonist'. Assuming the benzodiazepines to be full agonists, a number of partial agonists and antagonists have been described which fulfil conventional pharmacological criteria. Most interesting, however, are a range of compounds which act on the same receptors but possess pharmacological effects opposite to those of the benzodiazepines. These have been termed 'inverse agonists'. Within the partial agonists compounds may be found which have some but not all the effects of

the classic benzodiazepines. If this proves to be the case, anxiolytics or anticonvulsants without sedative effects or muscle relaxant properties may be developed.

The topic 'Psychopharmacology of cognition' reflects an area of enormous clinical importance, the dementias, where no effective medication exists at present. Accordingly, the lectures reflected recent advances in our understanding of the chemical pathology associated with profound cognitive dysfunction seen in dementia of Alzheimer's type AD. The degeneration of the forebrain acetylcholine system in AD is now well documented and for this reason there is considerable interest in the possibility of using cholinergic agents in the treatment of senile dementia. Basic cholinergic pharmacology in the CNS will now no doubt receive renewed attention, long overdue. Animal models of cognitive disorders will play an important role in the evaluation of potentially important new cerebroactive drugs. A wide range of behavioural tests are available from experimental neuropsychology to assess attention, perception, learning, and memory in rodents and in primates.

In the fourth session, 'Schizophrenia' was the focus of attention, and evidence relating to the aetiology, genetic basis, and neurochemical dysfunction in this disorder was discussed. An important principle emerged which would apply equally to depression or anxiety states – notably that inferring a neurochemical basis for a neuropsychiatric condition on the basis of the mechanisms of action of the drugs it responds to, may be misleading. Efficacious neuroleptics block dopamine receptors, but the evidence for heightened endogenous dopamine activity in schizophrenia is still highly contentious. Changes in post synaptic dopamine receptors may be secondary to other neurochemical changes in the brains of schizophrenic patients. Since a wide range of other monoamine transmitters and neuropeptides are known to interact functionally with the striatal and limbic dopamine pathways, this is a strong possibility. Furthermore, drugs which selectively modify these chemical pathways, for example antagonists of the neuropeptides substance P or neurotensin, could modify dopaminergic function as effectively as dopamine-receptor-blocking agents. It is clearly difficult to interpret neurochemical results on post-mortem brain tissue from drug treated patients, but such studies are of great importance in all neuropsychiatric conditions and hopefully will lead to a greater understanding of the primary neurochemical changes underlying these illnesses.

In the final symposium fundamental aspects of human psychopharmacology were discussed in a range of papers defining the effect of stimulant drugs on human performance. Inevitably, the issue of addiction was raised, since many of the psychostimulants which have beneficial effects in small doses, lead to detrimental effects when taken in larger doses and almost invariably to addiction. It was an appropriate finale to a review of modern psychopharmacology to be reminded that psychoactive drugs may improve brain function or restore dysfunction, but may also be instruments of self-destruction.

Harlow, Essex S. D. I.
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Contents

PART 1
Affective disorders

1

How effective are antidepressants?

E. S. PAYKEL

This chapter will survey the efficacy and place of antidepressants in the treatment of depression. I will range widely, but cannot be comprehensive. Space will not permit all the evidence, much of it from recent reviews (Paykel and Coppen 1979; Paykel 1982), on which the conclusions are based.

Akiskal and McKinney (1975) in an attempted synthesis, presented ten possible models of depression, ranging from the biological to the existential. These remind us that depressive disorder may be a final common pathway for multiple causes. It should not be expected that treatment would be limited only to the physical modality. A properly balanced presentation would allot full space to social and environmental measures, to psychotherapeutic and to behavioural approaches. These are beyond my mandate, but I will touch on controlled trials of psychotherapy and of cognitive therapy, to consider their place in relation to antidepressants.

Also, the term 'depression' covers a range of severity and other qualities from normal mood to severe psychotic illness. Recent prevalence figures for mild clinical disorder in women are around 5–10 per cent. Most see their general practitioners within the same year although they may not be diagnosed. Perhaps 90 per cent of depressives are treated in general practice, but almost all the evidence on treatment efficacy comes from psychiatric out-patients or in-patients. In a recent study (Sireling, Paykel, Freeling, Rao, and Patel, in press) we found that among antidepressant-treated patients in general practice only a half satisfied the Research Diagnostic Criteria for major depression, and only a third scored 17 or more on the Hamilton Depression Scale, both common inclusion criteria for psychiatric out-patient drug trials. More studies are needed of effectiveness and indications for treatments in such mild depressives.

In classification, the bipolar–unipolar division is obviously of value. However, most affective disorders are unipolar and here a broad separation into endogenous (or psychotic) and neurotic is still useful in treatment choice. The recent evidence is clear that symptom pattern is only very weakly related to absence or presence of stress, and it appears to be symptom pattern and severity rather than absence of precipitant stress which is associated with response to physical treatments (Paykel 1982; Paykel 1979).

ECT

Electroconvulsive therapy is still the touchstone physical treatment for severe depression against which all the other treatments must be measured. There have been five recent British double-blind controlled trials against simulated ECT with anaesthesia. The Knowle study found ECT only very weakly superior to placebo treatment. The Northwick Park study found effects that were clearly significant but not very strong. However, the Edinburgh, Sutton, and Leicester studies (Brandon, Cowley, McDonald, Neville, Palmer, and Wellstood-Eason, 1984), all found strong and conclusive effects. It is possible that the close care given to all patients in these difficult studies might mask greater differences in routine treatment. The study which showed the weakest effects employed unilateral brief pulse ECT. Robin and de Tiserra (1982) found brief pulse less effective than sine wave or high-energy pulse applications, and unilateral non-dominant ECT tends on average to be a little less effective than bilateral ECT (D'Elia and Raotma 1975).

With regard to who responds, eight predictor studies have shown that patients at the psychotic or endogenous extreme do better than neurotic depressives (Paykel 1979). Only two studies have failed to do so. The Northwick Park study found the best response in deluded depressives.

TRICYCLIC ANTIDEPRESSANTS

The tricylics have now been available for 25 years. They are well-studied drugs and there is no doubt of their overall superiority to placebo. Ten years ago Morris and Beck (1974) reviewed trials of the six tricyclics then available in the USA. There were 93 studies, of which 62 showed drugs superior to placebo and 31 failed to do so. This is far in excess of chance expectation of 5 per cent significance.

We do have the problem of the negative studies. Some are due to small samples, particularly with the variability in outcome common in depression, some to unresponsive subjects, low doses, or short treatment periods. Undoubtedly part of the problem also lies in limited efficacy. The spontaneous outcome of depression is often quite good, with added non-specific treatment effects from support and hospital admission. The element which the drugs add is on average limited, although it is very marked in some patients. The proportion of the total variance in antidepressant trials which is attributable to drug effects it is often quite low, around 10 per cent. Put another way, an additional 20-30 per cent of recoveries occur above those which might occur without the drug.

On the basis of early studies it has been claimed that endogenous depressives respond better than neurotic depressives to tricyclics. However, the evidence is not very clear-cut, even in the earlier studies (Paykel 1979). In recent years there have been many American reports that depressives with delusions do badly with