EDITIORIAL

Shifting depression

Biological studies into antidepressant drug action and into the aetiology of depression were highly active areas of research in the 1960s and 1970s but, arguably, have now lost some of their impetus and direction. Many investigations seem to have come to a natural end and there is a need for the subject to make a quantum leap to promote its development. It is recognized however, that advances have been made. Monoaminergic hypotheses of depression (Schildkraut, 1965; Coppen, 1967, for example) provided the basis of numerous clinical and laboratory investigations for over 25 years. From such studies, it was established that antidepressant drugs exert profound effects on noradrenergic (NA) and 5-hydroxytryptaminergic (5-HT) neurones in the central nervous system (CNS): they increase amine levels and/or their availability, they cause down regulation of several different receptor populations and they reduce the firing rates of central NA and 5-HT neurones arising from the locus coeruleus and the raphe nuclei respectively. Despite these discoveries, however, the information which is now available is related primarily to brain physiology and pharmacology rather than to the aetiology of depression or to the therapeutic action of antidepressants. It can even be argued on the basis of observations such as the fact that cocaine is a potent inhibitor of noradrenaline uptake and is not an antidepressant whereas iprindole is an antidepressant with no obvious effects on these monoaminergic systems, that many of the observed biochemical changes may be epiphenomena. Thus, some 35 years after the introduction of imipramine (Kuhn, 1958), the clinical perception of depression remains largely in the domain of the mind rather than the brain. Studies on urine, blood and CSF have provided extensive details on the metabolism of both neurotransmitters and drugs but, unfortunately, have been largely negative as far as providing markers for diagnosis of affective illness, for prediction of outcome or prediction of treatment response. In addition, numerous avenues of research have been pursued and abandoned. Nonetheless, substantial changes have been made: (a) in the way the CNS is conceptualized; (b) in the way drug trials are conducted; (c) in the way that diagnosis has become operational/descriptive rather than based on aetiological assumptions; (d) in the general management of patients; and (e) in our knowledge of the epidemiology of the problem. But equally, it has to be accepted that (for example) there is still no real clue to the mode of action of ECT or an explanation for the delay in onset of action of antidepressants. In addition, even with the introduction of 5-HT specific antidepressant drugs, the relative roles of 5-HT and NA in the aetiology of depression remain contentious: it is probable that with the introduction of serotonin specific re-uptake inhibitors (SSRI) such as paroxetine, fluoxetine and fluvoxamine into clinical use, the pendulum is at present swinging towards 5-HT. It is likely, however, that since serotonergic and noradrenergic systems are so interconnected anatomically, a clear separation of behavioural effects will remain elusive. There is, of course, the possibility that as new syndromal types are defined, association with one or other of the monoaminergic systems may emerge.

Considerable research over the last few years has been directed towards developing new drugs which have less side effects and a higher specificity for either NA or 5HT systems and to some extent this has been successful (Brunello et al. 1986; Dechant & Clissold, 1991). In parallel with these developments, there have been substantial advances in characterizing 5-HT receptor subtypes (Peroutka & Schmidt, 1991, for review) and the use of partial agonists of 5-HT-1A receptors as antidepressants has been proposed e.g. pyrimidinylpiperazines such as buspirone and ipsapirone. The

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development of reversible MAOIs (RIMAs) such as moclobemide and brofaromine have reduced
risks associated with consuming food containing tyramine although their efficacy as antidepressants
can still promote debate. Initiatives have also been made to examine the possible involvement of
other neurotransmitter systems, e.g. GABA and acetylcholine in the mode of action of
antidepressants. Finally, there are various ongoing studies attempting to develop antidepressant
drugs which act by altering the activity of receptor-linked second messenger systems (Campbell et al. 1987, for review): these include inhibitors of phosphodiesterase such as rolipram which would
increase intracellular cyclic AMP or inhibitors of inositol phospholipid turnover which,
theoretically, would have the same effect as lithium (Berridge & Irvine, 1989, for review).

As drugs with less side effects are developed, a clinical issue which has emerged is whether
antidepressant drugs should be used prophylactically (Montgomery & Montgomery, 1992, for
review). This question is important for several reasons: it is established that stopping drug treatment
prematurely leads to a high rate of recurrence of depression and also that in patients who have had
several previous depressive episodes, there is a substantial chance of relapse (Lee & Murray, 1988).
There are two issues: the first is continuance (i.e. there is a strong clinical case for treatment to be
extended for up to 6 months); the second is maintenance, in which case, the treatment may be
administered for years (see Kupfer & Frank, 1992, for review). Certainly, the use of antidepressants
in treatment regimens similar to those used with antipsychotics might provoke ethical questions
even if relapse rates are reduced. If these ideas are pursued, it raises the more academic question of
whether antidepressants cure or simply maintain a patient through a depressive episode: the latter
case would tend to negate existing biological hypotheses on the aetiology of depression.

There appears to be a growing need for clinicians and basic scientists to develop models of
depression containing elements of anatomy, physiology and pharmacology etc., in combination
with the clinical picture, i.e. the diagnosis (possibly to emphasize the heterogeneity of the disease),
the symptomatology, the genetics, the dimensionality of the condition, etc. Interestingly, in
schizophrenia research such integrative models are being developed (Swerdlow & Koob, 1987, for
example). However, as far as affective illness is concerned, this is not a trivial issue, but is important
because models would allow the development of new hypotheses and, hopefully, some movement
away from what currently seems to be a rather reductionist and restricted area of intellectual
endeavour in which it is difficult and probably oversimplistic to use existing biological models.

In parallel with the model building proposed above, new biological approaches are needed.
Although the involvement of monoamines seems apparent, there are still many inconsistencies and
unanswered questions. It should be possible to utilize the techniques of molecular biology to
determine the effects of various regimens of antidepressant drugs on gene expression in brain (i.e.
there is a case for moving from the constraints of hypotheses rooted in classical pharmacology).
This simply necessitates acceptance of the idea that drugs and other treatments such as ECT have
genomic effects in addition to those which they elicit on amine re-uptake (for example). When a wide
variety of stimuli, either physical, electrical (e.g. ECT), or chemical, are applied to the brain, changes
in gene expression occur either to complement or to correct for the effects of the stimulus: many
of these effects occur through the induction of a set of transcription factors, the immediate early
genes (IEG), for example, fos, jun, etc. (Cole et al. 1989; Wisden et al. 1990; Morgan & Curran,
1991). In addition to these factors, it is now established that classical receptor-linked second
messengers can also give rise to changes in gene expression. Thus, β-adrenergic receptor-linked
production of cAMP may activate a cyclic AMP response element binding protein (CREB) which
will alter gene expression (Haddock & Malbon, 1991). The idea that changes in gene expression are
aetiologically important in affective illness is also supported by the fact that hormones such as
cortisol which may have genomic effects on several systems are altered in depression and anxiety:
in this context, it is interesting to note that glucocorticoid receptor immunoreactivity in the locus
coeeruleus and raphe areas of rat brain are increased following imipramine treatment (10 µg/kg/2
weeks) (Kitayama et al. 1988).

There are probably many proteins whose production in the CNS which will be affected by
antidepressant drug administration: it is possible, therefore, that changes in novel systems would
produce new directions for depression and antidepressant drug research. It would be possible to examine: (a) the effects of acute versus chronic regimens; (b) clinically effective versus relatively ineffective drugs; (c) MAOIs versus tricyclics; (d) 5-HT versus NA specific drugs, and (e) effects occurring in brain areas not associated with depression (e.g. the corpus striatum). These various experimental strategies might, for example, allow the dissection of effects which were specific for antidepressant activity and not due to toxicity. Obviously, changes in the expression of several genes would occur, e.g. following chronic regimens, the expression of β-adrenergic receptors and 5-HT receptors would go down as might the expression of synthetic enzymes such as tyrosine hydroxylase.

Thus, experimentally, it would be necessary to screen for specific effects. Such investigations of the differential expression of messenger RNA (mRNA) could be undertaken using techniques such as subtractive hybridization (Palazollo & Meyerowitz, 1987) and the polymerase chain reaction (PCR) (White et al. 1989; Timblin et al. 1990; Leang & Pardee, 1992). The introduction of such methodologies in general biochemical/pharmacological of affective illness/antidepressant studies would, in addition, facilitate association between this area of investigation and molecular genetics.

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REFERENCES


