

## EDITORIAL

### Transmitter amines in depression<sup>1</sup>

This editorial comments on recent evidence concerning the roles in depression of the transmitter amines 5-hydroxytryptamine (5HT), dopamine (DA) and noradrenaline (NA). It focuses on evidence from brain chemistry and from effects of drugs used in treatment. The literature on urinary excretion of amine metabolites and on platelet erythrocyte and neuroendocrine abnormalities will not be discussed.

The transmitter amines account for only a small part of the neuronal population of the brain. Almost all of their cell bodies are in a small part of the brain stem. However, the widespread distribution and prolific arborization of their terminals suggest an importance for 'primitive' aspects of brain function which have been thought to underlie the broad disturbances of behaviour and mood characteristic of the major psychoses.

There is an increasing contrast between our knowledge of the complexity of brain transmitter amine systems and the simplicity of the questions with which most research on their significance for the psychoses has so far been concerned. On one hand, largely as a result of animal experiments, we know, or expect, multiple interactions of these transmitters with each other and with numerous other transmitter systems. We suspect that transmitter amines also have non-transmitter roles in the brain (Beaudet & Descarries, 1978; Jones, 1981) and we know of the multiplicity and modifiability of their receptors. Furthermore, it now seems that the long accepted 'one neurone – one functioning transmitter' rule is probably incorrect (Hokfelt *et al.* 1980; Osborne, 1981). If, on the other hand, we turn to the questions asked about amine abnormalities in psychoses, these are still 'do they exist?' and, if so, 'do they matter?', i.e. do they have roles in causation or are they secondary to other disturbances which do have causal roles, or to symptoms or to treatments?

No amine hypothesis of depression has had a simple history of increasing validation with time, although some difficulties of interpreparation no longer appear as great as they originally did when neurochemical ideas on psychoses mostly depended on a very narrow range of investigations and were based on assumptions such as 'one transmitter defect per gross diagnostic category'.

Some recent clarifications of old problems and the emergence of new ones and of new insights into the neurochemistry of depression are commented on below.

#### 5HT FUNCTION IN DEPRESSION

Research on the neurochemistry of depression continues to be dominated by brain 5HT findings but it becomes less easy to interpret these in terms of a causal role for 5HT deficiency, especially in view of the poor correlation between the therapeutic efficiency of antidepressants and their effects on 5HT function after chronic administration to rodents (Hall & Ogren, 1981; Ogren *et al.* 1979).

#### Decreased brain 5HT synthesis

Recent results (Gillman *et al.* 1981; Huet *et al.* 1981) strengthen earlier indications that plasma free rather than total tryptophan (free plus albumin-bound) influences the availability of tryptophan to the brain and hence influences synthesis and, in some circumstances, functional activity (Kennett & Joseph, 1981) of 5HT. It therefore remains of interest that plasma free tryptophan was low in some groups of patients with post-partum and other depressions (Stein *et al.* 1976; Handley *et al.* 1980; Swade & Coppen, 1980). While this has not been confirmed for other depressives (Moller *et al.* 1979), some of the latter were found to have low plasma ratios of tryptophan to amino acids

<sup>1</sup> Address for correspondence: Professor G. Curzon, Institute of Neurology, 33 Johns Mews, London WC1N 2NS.

which can compete with its uptake by the brain (Moller *et al.* 1980). Although low plasma tryptophan in depression could be primarily a consequence of depressive symptoms (Curzon *et al.* 1979; Shaw *et al.* 1980), it might nevertheless alter the course of the illness.

Decreased brain 5HT turnover is more directly indicated by the low lumbar CSF concentrations of its metabolite 5-hydroxyindoleacetic acid (5HIAA) which have been reported in many studies (e.g. Goodwin & Post, 1975; Curzon *et al.* 1980*b*), although some investigators disagree (e.g. Berger *et al.* 1980). Low values probably indicate that 5HT turnover is low in part of the nervous system only as ventricular CSF 5HIAA appears normal (Curzon *et al.* 1980*b*). It may be relevant that Lloyd *et al.* (1974) found low 5HT values in the dorsal and inferior central raphe but not in other brain stem regions of depressive suicides. Birkmayer & Riederer (1975), however, report a marked and widespread brain 5HT defect in autopsy material from depressives.

Disagreements on lumbar 5HIAA in depression may derive from differences in patient selection, as Åsberg *et al.* (1976) found that values were distributed bimodally. Patients in the low 5HIAA mode attempted suicide more often and more violently than those in the high mode. Somewhat similar results were obtained by Agren (1980) (who also obtained low values for the NA metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG)). Also, Banki *et al.* (1981) found that severely depressed females with relatively low lumbar CSF 5HIAA had significantly greater scores for suicidal behaviour, anxiety, agitation and insomnia than a group with relatively high values. Significant differences for the DA metabolite homovanillic acid (HVA) were in the opposite direction (see below). The 5HIAA results are reasonably consistent with evidence for roles of 5HT in sleep (Jouvet, 1977), motor activity (Marsden & Curzon, 1976) and responsiveness to stimuli (Waldbillig *et al.* 1981). This suggests that the abnormality of 5HT metabolism has causal significance for symptomatology (see below for discussion of the HVA findings). Another recent indication that different depressive subgroups may have differences of central 5HT metabolism comes from Rosenthal *et al.* (1980), who found that depressed patients with alcoholism in a first-degree relative had significantly lower CSF levels of 5HIAA than those without this family history. MHPG was similarly decreased.

### Evidence from treatments

If brain 5HT deficiency has a causal role in depression then treatments which increase 5HT synthesis or increase responses dependent on 5HT should have a therapeutic effect. Whether tryptophan given alone is effective has been the subject of controversy. While some authors report it as being not inferior to conventional treatments (e.g. Lindberg *et al.* 1979) others disagree. However, it is generally agreed to potentiate other antidepressants such as MAO inhibitors (Coppen *et al.* 1963) and the 5HT re-uptake blocker chlorimipramine (Wålinder *et al.* 1976), which suggests that their therapeutic effects depend on 5HT. Also, involvement of 5HT in the antidepressant action of tranlycypromine is indicated by its prevention by the 5HT synthesis inhibitor *p*-chlorophenylalanine (Shopsin *et al.* 1976). Furthermore, tryptophan and other antidepressants tending to increase 5HT functional activity are particularly effective in patients with evidence of a 5HT defect (Moller *et al.* 1980; Van Praag, 1977). These findings, together with the indications that ECT may increase 5HT function (Green, 1980; Lebrecht & Nowak, 1980) and that 5-hydroxytryptophan, the immediate precursor of 5HT, is prophylactic against depression (Van Praag & De Haan, 1980), all point to a deficiency of brain 5HT synthesis being responsible in some way for depressive illness in at least a considerable subgroup of patients.

Doubt has now been cast on this interpretation: although acute effects in animals of many antidepressants (or substances under test as antidepressants) are consistent with them increasing 5HT functional activity, there are numerous exceptions and also a number of chronic effects suggest otherwise. As, in general, benefit only occurs after chronic drug treatment, such findings (e.g. that antidepressants *decrease* 5HT functional activity) may be more relevant to therapeutic action. Thus, in rodents, Fuxe *et al.* (1981) found that chronic administration of the 5HT re-uptake inhibitor zimelidine to rats decreases high affinity <sup>3</sup>H [5HT] and <sup>3</sup>H [LSD] binding sites, decreases 5-hydroxytryptophan-provoked head twitches, and decreases the secretion of 5HT dependent

neuropeptides. Also, a large number of low affinity  $^3\text{H}$  [5HT] and  $^3\text{H}$  [LSD] binding sites appear. Somewhat similar results were also obtained following chronic treatment with imipramine or desipramine (Ogren *et al.* 1982).

Chronic administration of the 5HT re-uptake inhibitor and putative antidepressant fluoxetine is also reported to decrease 5HT binding sites and the affinity of 5HT for them (Wong & Bymaster, 1981). Other binding studies with a number of antidepressants point in the same direction (Fillion & Fillion, 1981; Keller *et al.* 1981). These results are consistent with hypotheses of a causal role for 5HT post-synaptic receptor hypersensitivity in depression – for example, that of Aprison *et al.* (1978) in which hypersensitivity develops as a compensatory response (perhaps to the known pre-synaptic deficiency) so that depression occurs when some unknown precipitant causes an abnormally large 5HT release and hence overcompensation.

Such hypotheses suggest that 5HT synthesis inhibitors should be antidepressants. Indeed, *p*-chloro-*N*-methylamphetamine, which causes a prolonged decrease of 5HT synthesis in rats (Fuller & Molloy, 1974), gave encouraging results in a pilot trial (Van Praag *et al.* 1969). However, drugs of this type are also acute 5HT releasers and it is not clear which action was involved in the beneficial effect. Interpretation of the antidepressant effects of 5HT receptor blockers such as pizotifen, danitracen, mianserin and doxepin is also difficult because of the other actions of these drugs (Maj *et al.* 1977).

It is not yet possible to decide between the two 5HT hypotheses, but it must be stated that much evidence still favours a more directly causal role for 5HT deficiency. First, some authors find that chronic treatments with 5HT re-uptake inhibitors do not alter binding sites (Hwang *et al.* 1980; Ross *et al.* 1981). Secondly, many antidepressants (imipramine, desipramine, amitriptyline, pizotifen and mianserin) enhance behavioural effects of 5HT in the chick after chronic administration (Jones, 1980). Thirdly, the potentiation of the antidepressant effect of MAO inhibitors by tryptophan (Coppen *et al.* 1963) is most easily explained in terms of increased availability of 5HT (or perhaps tryptamine – see Marsden & Curzon, 1979). Similarly, ECT treatment probably tends to enhance responses to 5HT (Green, 1980; Lebrecht & Nowak, 1980). ECT studies in animals suggest that the latter effect could involve increased activity of noradrenergic neurones ‘beyond’ the 5HT receptors (Green & Deakin, 1980) and/or increased 5HT<sub>2</sub> receptors (Keller *et al.* 1981), though the finding by these workers that various antidepressant drugs given chronically had an opposite effect then becomes less easy to explain.

Very recent work on the effects of antidepressants on receptors (Ogren *et al.* 1982) could indicate that these drugs correct *both* hypo- and hyper-responsiveness to 5HT which implies that either abnormality may lead to the development of depression. Finally, it should be emphasized that all the above animal findings only provide suggestive analogies. Final conclusions about the neurochemistry of depression demand post-mortem receptor studies.

## DA FUNCTION IN DEPRESSION

The question of whether DA disturbances are important in depression has been revitalized by Bank *et al.* (1981), who report that severely depressed patients with relatively high lumbar CSF concentrations of HVA had significantly higher scores for anxiety, insomnia and agitation, and significantly lower scores for fatigability and retardation than did a group with relatively low values. These results, if taken together with the concurrently determined CSF 5HIAA values previously mentioned, are consistent with the general concept of ergotropic and trophotropic roles for the catecholamines and 5HT respectively (Brodie & Shore, 1957). They are also consistent with roles for DA in the mediation of motor activity, arousal and sensory and consumatory responses (Kelly, 1977; Antelman *et al.* 1975). However, a different explanation of certain associations between DA metabolism and symptoms is suggested by earlier work by Post *et al.* (1973), who showed that lumbar HVA values could alter as a *consequence* of altered psychomotor activity.

Nevertheless, a causal involvement of DA deficiency in retardation is suggested by its alleviation by nomifensine (which predominantly enhances DA-ergic transmission) but not by chlorimipramine

(which has little effect on DA systems) (Van Scheyen *et al.* 1977). Furthermore, a DA agonist, piribedil, and a DA antagonist, pimozide, are reported to be beneficial in depression and mania respectively (Post *et al.* 1978, 1980). The piribedil study is of particular interest, as benefit correlated significantly with pre-treatment DA deficiency as indicated by CSF HVA values. Another indication that antidepressant treatments can involve enhanced DA-ergic transmission comes from the decrease of nigral DA autoreceptor sensitivity when rats are either given various antidepressants chronically or subjected to electroconvulsive shock (Chiodo & Antelman, 1980; Serra *et al.* 1981).

## NA FUNCTION IN DEPRESSION

The historical development of ideas on the roles of NA and 5HT in depression have followed rather similar courses. Thus, early work on NA emphasized a causal role of decreased NA synthesis (Schildkraut, 1973) but some subsequent findings on the chronic effects of antidepressants in animals led to an alternative hypothesis, suggesting that if decreased NA synthesis occurred it was merely secondary to abnormally high post-synaptic receptor sensitivity (Sulser, 1978). As with 5HT, the present position is not entirely clear.

In general, urinary abnormalities are not being discussed in this editorial. However, deductions of decreased brain NA synthesis from urinary determinations of MHPG demand a brief comment since, although this has been used as an index of central NA turnover, most evidence suggests otherwise (Karoum *et al.* 1974; Crawley *et al.* 1980). CSF MHPG values do reflect brain NA metabolism, and while most investigators have obtained normal values (e.g. Berger *et al.* 1980), subgroups with low values may exist (Rosenthal *et al.* 1980). Also, Agren (1980) found significant negative correlations between MHPG and various measures of suicidal tendency in a group of unipolar depressives.

The antidepressant effects of the NA re-uptake inhibitor, maprotiline (Maitre *et al.* 1975), and the  $\beta$ -agonist, salbutamol (Hallberg *et al.* 1981), are most readily interpretable in terms of a causal involvement of an NA-ergic deficiency in the illness. Similarly, animal experiments suggest that ECT alters central NA function. However, it would be possible to interpret some of these data as evidence for *increased* NA function in depression (see the review by Waldmeier, 1981).

## RELATIONSHIPS BETWEEN DIFFERENT TRANSMITTER AMINE ABNORMALITIES AND DEPRESSION

The most cautious analysis of the available data must lead to the conclusion that disturbances of 5HT, DA and NA function occur in at least some groups of patients with depressive illness and are involved in its precipitation, symptom pattern or course. Evidence also points to the mediation of different symptoms by different transmitter defects (Åsberg *et al.* 1976; Agren, 1980; Banki *et al.* 1981) and to associations of some defects with familial disposition to depressive illness (Rosenthal *et al.* 1980; Sedvall *et al.* 1980).

Another possibility is that different transmitter defects on the same common pathway may, in different patients, lead to similar symptomatology. That this may occur is indicated by numerous animal experiments. Thus, behavioural effects of 5HT receptor activation are influenced by drugs which act on NA-ergic, DA-ergic, cholinergic or GABA-ergic systems (Green & Deakin, 1980; Curzon *et al.* 1980a). Finally, it should not be assumed that abnormal interactions between transmitters in depression exclusively alter broad behavioural categories in the manner implied by the classical ergotropic-trophotropic hypothesis (Brodie & Shore, 1957). For example, recent animal work on behavioural effects of 5HT-DA interactions (Andrews *et al.* 1982) describes not only motor behaviour which is induced by DA and inhibited by 5HT (consistent with the above hypothesis), but also other forms of behaviour which are induced by 5HT but inhibited by DA, and still others which require both transmitters.

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