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COMMENTARY

MODE OF ACTION OF ANTIDEPRESSANT DRUGS*

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The current catecholamine and/or idolealkylamine hypothesis

Despite the widespread use of antidepressant drugs, the precise mechanism of their antidepressant action in man remains to be elucidated. It has been generally accepted, however, that at least part of the therapeutic action of antidepressants drugs [tricyclic antidepressants and monoamine oxidase (MAO) inhibitors] may be the consequence of an increased availability of norepinephrine (NE) and/or serotonin (5-HT) at post-synaptic receptor sites. The question of whether the clinical antidepressant activity is more closely related to the effect of the drugs in increasing the availability of NE or of 5-HT is difficult to answer because MAO inhibitors increase the availability of both monoamines, and tricyclic antidepressants affect transport mechanisms of both amines or are *in vivo* converted to metabolites which in concert with the parent drug will inhibit both systems. Moreover, some of the antipsychotic agents have also been reported to exert potent blocking effects on both uptake systems [1, 2]. If differences in the relative degree of blocking uptake of NE of 5-HT are indeed of clinical significance, the availability of, and controlled clinical trials with more selective inhibitors, such as maproptiline and nisoxetine (preferential inhibitors of NE uptake) and FG 4963 [3], Lu 10-171 [4] and fluoxetine (preferential inhibitors of 5-HT uptake), should provide a more definite answer to this problem. Fluoxetine is of particular interest because this drug is a selective inhibitor of 5-HT uptake into specific brain regions *in vivo* and *N*-demethylation to its primary amine does not alter either its potency or selectivity toward inhibiting uptake of 5-HT [5]. While Wålinder *et al.* [6] reported a more rapid improvement of depressive symptomatology in a double blind study with chlorimipramine and tryptophan as compared to chlorimipramine + placebo, and Shopsin *et al.* [7, 8] found that the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine reversed the antidepressant effects of both MAO inhibitors and tricyclic antidepressants, the potentiation by tryptophan of the antidepressant action of tricyclic antidepressants remains equivocal [9, 10]. Moreover, clinical studies with a more selective inhibitor of 5-HT uptake, FG 4963, have so far not been very encouraging [11].

Results obtained with the tricyclic antidepressant iprindole and with mianserin raise additional questions about the current biogenic amine hypothesis of affective disorders. Iprindole is reported to be a clinically effective antidepressant [12–14], but, unlike imipramine-like drugs, this drug does not block the neuronal uptake of NE [1, 15–18] and it does not alter the metabolism of NE [17] or the turnover of NE [18] or 5-HT [19]. Also, Nybäck *et al.* [20] found that, while other tricyclic antidepressant agents suppressed the spontaneous firing rate of NE cells in the locus coeruleus, iprindole was unique in that it lacked this ability, indicating that it did not increase NE at post-synaptic receptor sites. Obviously, the blockade of reuptake of catechol- and/or indolealkylamines is not an absolute prerequisite for antidepressant activity of a drug. Coppen *et al.* [21] have shown that the therapeutic efficacy of mianserin HCl was similar to that of amitriptyline in dosages that did not influence the reuptake of amines. Though apparently difficult to reconcile with the classical biogenic amine hypothesis of affective disorders, these data do not necessarily rule out an interaction with noradrenergic or serotonergic mechanisms, for example at the receptor level.

Acute pharmacological effects vs therapeutic action of antidepressant drugs

The heuristic catecholamine hypothesis of affective disorders [22, 23] is chiefly derived from studies on acute pharmacologic effects elicited by a number of clinically effective antidepressant drugs and usually does not take into consideration the discrepancy in the time course between biochemical and pharmacological effects elicited by, for example, tricyclic antidepressants within minutes and their clinical therapeutic action which generally requires treatment for several weeks. Recently, Segal *et al.* [24] have reported adaptive changes in the activity of tyrosine hydroxylase that are inversely correlated with changes in the availability of catecholamines. Thus, chronic administration of desipramine for 8 days produced a significant decrease in the activity of the enzyme in the locus coeruleus and hippocampus-cortex area, while chronic administration of reserpine caused a marked increase in the activity of tyrosine hydroxylase. Such adaptive changes in the biosynthetic capacity may explain the decrease in the level of NE observed after chronic [25, 26] but not acute administration of tricyclic antidepressants [27, 28]. The findings might also offer an explanation for the observed decreased rate of turnover of brain NE after chronic administration of tricyclic antidepressants to rats [29]. However, Schildkraut *et al.* [25, 30] have provided data that are consistent with the view that chronic treatment with tricyclic antidepressants enhances the turnover of NE. Differences in the methodology used to assess

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turnover might in part be responsible for the discrepancies in results.

There is some evidence to suggest that prolonged treatment with tricyclic antidepressants can affect other amine systems. For example, chronic treatment with imipramine for 10 days has been reported to decrease the levels of 5-HT and 5-HIAA in the mesodiencephalon, pons-medulla oblongata and hippocampus of rat brain [31]. While no significant changes in the levels of NE were found, the levels of dopamine (DA) were increased in cerebellum and pons-medulla oblongata and decreased in striatal regions. With the exception of nomifensine which has been reported to be a potent inhibitor of DA uptake [32], tricyclic antidepressants exert only weak effects on DA uptake in synaptosomal preparations of rat brain [33].

Effect of tricyclic antidepressants on MAO activity

Since not all tricyclic antidepressants have been found to block uptake of NE and/or 5-HT, other possible mechanisms for their action have been explored. Imipramine and amitriptyline have been previously reported to inhibit liver MAO *in vitro* [34]. More recent work using rabbit lung and brain MAO and human platelet MAO suggests that many tricyclics inhibit type B of the enzyme *in vitro* [35–37]. Some work indicates that classical MAO inhibitors (tranylcypromine and pargyline) with antidepressant properties are also selective for type B MAO in rat brain using phenylethylamine (PEA) and 5-HT as substrates [38]. However, another report using benzylamine and 5-HT as substrates indicates that tranylcypromine is not selective [39]. Also, clorgyline, which has been reported to have antidepressant properties [40], appears to be selective for type A MAO [39].

The selective action of many antidepressants on type B MAO has added to the interest in a role for one of its endogenous substrates, PEA, in depression. Fischer *et al.* [41] found that the urinary excretion of PEA was reduced in depressed subjects. Imipramine increased the levels of PEA in brain as did pargyline and iproniazid [42, 43]. Also, it has been reported that platelet MAO (type B) appears to be higher in depressed patients [44]. Von Voigtlander and Losey [45] determined if antidepressants alter the metabolism of PEA *in vivo*. Their studies showed that neither acute nor chronic treatment with imipramine, iprindole or amitriptyline blocked the disappearance of labeled PEA, while a single dose of pargyline, tranylcypromine and nialamide caused a marked increase in labeled PEA in brain. In the absence of confirmation *in vivo*, the pharmacological significance of the reported inhibition of MAO by tricyclic antidepressants *in vitro* remains unknown.

The noradrenergic cyclic AMP generating system in the limbic forebrain—a functional post-synaptic NE receptor system and its modification by drugs which either precipitate or alleviate depression

Since 1974, our research group has been concerned with NE–receptor interactions in the limbic forebrain and their modification by psychotropic drugs which either can precipitate or alleviate depressive reactions in man. We have chosen as a functional model the noradrenergic cyclic AMP generating system of the limbic forebrain [46–49] because this particular cyclic AMP generating system displays a number of characteristics which are compatible with those of a central NE receptor. For neurophysiological and neurochemical reasons, the limbic forebrain appears to be a topographical target of choice as this area provides a key integrating system related to selective modulation of emotion and sensory mechanisms of the brain [50] and receives noradrenergic input originating in cell bodies of the pons and medulla oblongata, dopaminergic fibers from the A-10 region and serotoninergic fibers from the anterior raphé complex [51, 52].

Functional modification of the NE receptor coupled cyclic AMP generating system by drugs which can precipitate despair or depression. Several behavioral studies have suggested an enhanced receptor reactivity to intraventricular NE after reserpinization or chemical sympathectomy with 6-hydroxydopamine (6-OHDA) [53, 54]. An increased responsiveness of the cyclic AMP generating system to NE after 6-OHDA in cortical slices [55–58] or in slices from the hypothalamus and brain stem [59] has also been reported.

The sensitivity to NE of the specific noradrenergic cyclic AMP generating system in the limbic forebrain is increased approximately 4-fold after destruction of noradrenergic nerve terminals with 6-OHDA [60]. The changes in the reactivity of the cyclic AMP generating system appear to be related to changes in the availability of NE and not to those of other neurohormones, as protection by desipramine of noradrenergic neurons against the neurotoxic action of 6-OHDA prevented the development of hypersensitivity of the system to NE. The enhanced responsiveness of the cyclic AMP generating system to NE after chemosympathectomy with 6-OHDA appears in all probability to be the consequence of changes occurring at post-synaptic noradrenergic receptor sites and are not the consequence of pre-synaptic events such as blockade of neuronal uptake into pre-synaptic nerve terminals. Thus, the sensitivity to isoproteronol which is not taken up by pre-synaptic nerve terminals [61] is also enhanced after chemosympathectomy with 6-OHDA.

It does not seem likely that the enhanced responsiveness is related to changes in the activity of phosphodiesterase, as the response to adenosine remained unchanged after 6-OHDA. Moreover, Kalisker *et al.* [58] found only minor changes in the activity of cyclic AMP phosphodiesterase under conditions of enhanced sensitivity to NE after 6-OHDA and, in the presence of high concentrations of effective phosphodiesterase inhibitors, the accumulation of cyclic AMP elicited by NE or isoproterenol was still significantly higher in cortical slices from rats treated with 6-OHDA [57].

Subchronic treatment with reserpine also enhances the response to NE in slice preparations from the limbic forebrain, while not changing the basal level of the nucleotide [60]. Reserpine and 6-OHDA do not appreciably change the affinity of NE to the receptor as judged from the EC_{50} values. It is tempting to speculate that prolonged deprivation of NE at post-synaptic sites may change the actual number of

receptors. The increased sensitivity of adrenergic β-receptors in rat cerebral cortex after 6-OHDA has been shown to be associated with an increase in the density of β-adrenergic receptors [62].

The sensitivity of the NE receptor coupled adenylate cyclase system in slices of the limbic forebrain is also increased after lesions of the medial forebrain bundle (unpublished observations). Similar enhanced cyclic AMP responses to NE after lesions of the medial forebrain bundle have been observed in rat cortical slices [63]. As treatment with 6-OHDA and particularly with reserpine has been shown to either cause behavioral changes in monkeys resembling despair and depression [64, 65] or to precipitate severe depressive reactions in man [23, 66], the common change caused by these drugs in the post-synaptic NE receptor coupled adenylate cyclase system in the limbic forebrain is of considerable theoretical interest.

Effect of various antidepressant treatments on the sensitivity of the NE receptor coupled cyclic AMP generating system in the limbic forebrain. Since drugs which can precipitate depression caused an enhanced receptor sensitivity to NE, studies on the effect of antidepressant drugs on this system, particularly when administered on a clinically more relevant time basis, were of interest. While a single dose of desipramine (DMI) and iprindole or short time treatment with tricyclic antidepressants did not alter the basal level of the cyclic nucleotide or the neurohormonal response to NE, the administration of these drugs for 3–6 weeks lead to a marked reduction in the sensitivity of the noradrenergic receptor coupled adenylate cyclase system [67]. The decreased hormonal sensitivity to NE appears not to be a direct effect of the drugs, as no correlation exists between the concentration of the drugs in brain tissue and the change in the cyclic AMP response to the catecholamine. The development of a delayed subsensitivity after the chronic administration of tricyclic antidepressants has been confirmed recently by Schultz [68]. He has shown that chronic but not acute administration of imipramine causes subsensitivity of the NE stimulated formation of cyclic AMP in rat brain cortex. The finding that this effect was shared by chlorpromazine is not surprising, as chlorpromazine also increases the availability of NE at post-synaptic sites (pre-synaptic α-blockade, blockade of NE reuptake), thus sharing pharmacological properties with classical tricyclic antidepressants.

Chronic but not acute administration of MAO inhibitors also caused a marked decrease in the reactivity of the noradrenergic receptor coupled adenylate cyclase system, a decrease which was unrelated to the size of the store of the catecholamine [60]. Preliminary results show that withdrawal of the MAO inhibitors for 9 days after treatment for 3 weeks results in normalization of the neurohormonal response. These data indicate the ability of "normal" post-synaptic receptors to adapt to a prolonged increase in the availability of NE and provide evidence for an important regulatory mechanism involving the noradrenergic receptor coupled adenylate cyclase system in the limbic forebrain. MAO inhibitors thus share this delayed action on the noradrenergic receptor coupled adenylate cyclase system in the limbic forebrain with tricyclic antidepressants.

Since electro-shock treatment (ECT) is one of the most effective treatments for severe depression and the onset of its therapeutic action is generally considered to be more rapid than that after pharmacotherapy, we were curious to investigate the effect of this non-drug treatment on neurohormonal responses to NE. Daily administration of ECT for 8 days reduced the cyclic AMP response to NE by approximately 50 per cent and the reduced responsiveness was still significant 7 days after cessation of ECT [67]. The decreased responsiveness to NE after ECT may explain the reported antagonism by ECT of the stimulatory effect elicited by the combined administration of desipramine and the benzoquinolizine derivative RO 4-1284 [69] or after amphetamine [70], since the stimulatory effect of these drugs or drug combinations is thought to be due to the release of catecholamines onto post-synaptic receptor sites.

The decreased noradrenergic receptor function resulting from prolonged treatment with MAO inhibitors, tricyclic antidepressants (imipramine-like and iprindole) and after the administration of ECT suggests that the therapeutic action of antidepressants may be related to the common delayed post-synaptic sensitivity changes of the receptor coupled adenylate cyclase system rather than to their acute and often opposite pharmacologic effects elicited at pre-synaptic sites. It is of considerable interest in this regard that ECT partially prevented the reserpine-induced increase in receptor sensitivity and significantly alleviated the already developed hypersensitivity of the NE receptor system [67].

A revised catecholamine hypothesis of affective disorders and a new interpretation of the mode of action of some antidepressant drugs

The findings that psychotropic drugs which either can precipitate (reserpine, 6-OHDA) or alleviate despair and mental depression (imipramine-like tricyclic antidepressants, iprindole, MAO inhibitors, and ECT) cause opposite changes in the reactivity of the limbic noradrenergic receptor coupled adenylate cyclase system suggest a new theoretical framework for studies on the psychobiology of depression. If nothing else, the studies shift the emphasis on mechanisms of action of antidepressant drugs from pre-synaptic to post-synaptic receptor mediated events. Research over the next several years will undoubtedly be focused on the molecular mechanisms of regulation of central noradrenergic receptor activity including β-adrenergic receptors and NE receptors which are not β in nature. Based on studies of pre-synaptic alterations of the biosynthetic capacity of catecholaminergic neurons after chronic administration of psychotropic drugs, Mandell *et al.* [24, 71] have speculated that depression might be viewed as a reflection of a state of pathologic hypersensitivity of catecholaminergic receptors in brain. Studies with reserpine and 6-OHDA now provide experimental evidence for such an assumption at the level of the NE receptor coupled adenylate cyclase system in the limbic forebrain. Clinically, both mania and depression are characterized by a chronic state of hyperarousal [72, 73]. Based on the effect of antidepressant treatments on post-synaptic noradrenergic receptor function, it is tempting to speculate that antidepressant drugs and ECT

bring about a desensitization of enhanced noradrenergic receptor function, thus causing a reduction in the postulated amplification mechanism that translates sensory input eventually into physiological and behavioral events. Within the context of such thinking, the low levels of catecholamine metabolites in the cerebral spinal fluid of endogenously depressed patients [74, 75] could be viewed as the consequence of a receptor mediated compensatory decrease in the biosynthetic activity rather than as related to the cause of depression. The clinical biochemical findings that treatment with tricyclic antidepressants is associated with a slight increase in MHPG in the cerebral spinal fluid among responders but causes a significant further decrease among non-responders [74–76] are compatible with such a hypothesis. Only therapeutic successful desensitization of hypersensitive NE receptors would lead to a reduction in feedback inhibition of the biosynthesis of NE, while failure to do so would tend to activate feedback mechanisms as a consequence of the increased availability of NE at hypersensitive receptor sites. In the context of such suggestions, the lack of large doses of l-DOPA to rapidly reverse depressive symptomatology [66] might not be so surprising.

A revised catecholamine hypothesis of affective disorders which takes into consideration the crucial neurohormone–receptor interactions will have new heuristic values, as it will focus psychopharmacological research on the molecular mechanisms involved in the translation of neurohormonal messages into intracellular events and raise exciting new questions on the molecular genetics of depressive illness.

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