UPDATE ON THE MECHANISM OF ACTION OF ANTIDEPRESSANT DRUGS

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From therapeutic effectiveness and their possible mode of action of the antidepressants, three main postulated biochemical theories underlying the depressive illness have been developed. They are:

1. The central monoamine-deficiency hypothesis:

The etiology of the illness is believed to be an absolute or partial deficiency of norepinephrine (NE) and serotonin(5HT) centrally. This based on the evidence that drug like reserpine, which depletes central monoamines, could precipitate the illness while drugs like tricyclic antidepressants, monoamine oxidase inhibitors and tryptophan, which elevate the central monoamines relieve the symptoms.

2. The adrenergic supersensitivity hypothesis:

It is postulated that supersensitivity of central adrenergic receptors is the cause of the illness. Therefore, antidepressants exert their actions by down-regulation of the sensitivity of the adrenergic receptors as is evident by the association between the chronic antidepressant administration and the adaptive changes in central adrenergic receptors.

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3. The cholinergic hypothesis:

The imbalance between the central catecholamine and cholinergic systems would lead to the symptomatic affective disorders. When cholinergic activity predominates depressions is the consequence, and mania results when catecholamine activity is predominant. Reserpine causes depression by lowering central catecholamines levels and thus cholinergic activity is enhanced.

The classical amine hypothesis seems to be receiving more and more questions concerning its validity during the past decades. This is probably due to the inconsistency of clinical data together with the apparent objections on effectiveness of the antidepressants. Several shortcomings on this hypothesis have been addressed as followings: a) the discrepancy of the time course between biochemical and pharmacological effects elicited by antidepressant treatments like tricyclic antidepressants; b) the marked variations in clinical responses despite a uniform pharmacologic inhibition of reuptake of monoamines; c) not all antidepressants inhibit reuptake of monoamines but show clinical effectiveness such as mianserin, iprindole; d) not all inhibitors of monoamine reuptake have antidepressive activity, e.g. cocaine; e) tricyclic antidepressants have multiple sites of action.

Most of the works today try to characterize the binding of the tricyclic antidepressants on the nerve terminals. Some tricyclic antidepressant exhibits specificity toward binding on noradrenergic or serotonergic neurons. However, subcellular studies of the animal brains indicated that the binding sites of these tricyclic antidepressants were not assosi-

ated with their respective inhibition of monoamine reuptake. Furthermore, it is possible that the abnormalities of the events in monoamine nerve terminals such as synthesis, storage, release and reuptake may contribute to the etiology of the illness. But the evidence obtained so far never convincingly demonstrated that defect in these events is operative in the etiology of affective disorders. Thus the search for biochemical markers of this disease has shifted from presynaptic to postsynaptic mechanisms.

The cholinergic theory is far less acceptable because most clinically effective newer antidepressants are relatively lack of the anticholinergic property as usually seen in the typical antidepressants. In fact, this anticholinergic property is believed to be related more to the side effects of the drugs rather than to their mechanism of action. Therefore, details on those two mentioned theories will not be discussed here.

Current data concerning methodology and problems in elucidation of the down-regulation of adrenergic receptors is present in this review.

Down-regulation of beta-adrenergic receptors and antidepressant action

This phenomenon was first reported in 1974 by Alan Frazer and his colleagues and by Fridolin Sulser's group. They observed a consistent result in down-regulation of the beta-adrenergic receptors in slices of rat cerebral cortex and limbic forebrain following chronic treatment with imipramine, desipramine(DMI) and iprindole. The mechanisms responsible for these adaptive changes in receptors as well as their significance to the clinical antidepressive actions are currently under intense investigation.

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This down-regulation mechanism is evident by a reduction of Bmax values of beta-adrenoceptors in the brain without significant changes in the Kd values following chronic antidepressant administrations. Since beta-adrenoceptors in brain tissues are coupled to adenylate cyclase system alteration on the receptors should therefore be an indicative of the change in enzyme activity. This has been proved to be the case as many antidepressant treatments elicit subsensitivity of the NE-sensitive adenylate cyclase in the brain and/or down-regulate the beta-adrenoceptors as shown in Table 1.

It has been proposed that this down-regulation of beta-adrenergic receptors may account for the antidepressive action. In order to prove this hypothesis most experiments were conducted as a long-term treatment in animal models. This is due to the observation that the onset of the beneficial effect of antidepressant is clinically seen after 2-3 weeks of drug administrations.

In general the research strategies that have been used by most investigators to prove the addressed hypothesis can be classified into 2 types.

a) In vitro radioligand binding studies

Brains of chronically treated animals were used. Crude synaptic membrane was prepared from the treated brains and was incubated with various concentrations of the labeled beta-antagonist, usually ^{3}H-dihydroxyalprenolol (^{3}H-DHA), to obtain the total binding activity; the non-specific binding was measured by incubation of the homogenate with certain

TABLE 1 *Effect of antidepressant treatments on the NE-receptor-coupled adenylate cyclase system in brain.*

Treatments	Subsensitivity to NE	Down-regulation of β-adrenoceptors
MAO inhibitors		
Pargyline	Yes	Yes
Nialamid	Yes	Yes
Tranylcypromine	Yes	Yes
Clorgyline (A)	Yes	Yes
Deprenyl (B)	No	No
Inhibitors of 5-HT and/or NE uptake		
Amitriptyline	Yes	Yes
Imipramine	Yes	Yes
Clorimipramine	Yes	Yes
Zimelidine	Yes	Yes
More selective inhibitors of NE uptake		
Desipramine	Yes	Yes
Nortriptyline	Yes	Yes
Oxaprotiline	Yes	Yes
Electroconvulsive treatment	Yes	Yes
REM sleep deprivation	-	Yes
Other potential antidepressants		
Iprindole	Yes	Yes
Mianserin	Yes	No; Yes
Fluoxetine	No	No
Trazodone	?	?
Bupropion	?	?

MAO, monoamine oxidase; 5-HT, serotonin; REM, rapid eye movement. (After (1))

concentration of ^{3}H-DHA in the presence of approximately 1000 folds greater in concentration of unlabeled alprenolol or propranolol. The density of the receptors and the affinity of the binding were then elaborated from the Scatchard analysis.

b) Beta-adrenergic-sensitive adenylate cyclase studies

One of the functional response to beta-receptor stimulation by

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adrenergic drugs is the increase in cAMP formation due to an increase in adenylate cyclase activity residing in that tissue. Therefore, most data presented usually include the ability of antidepressant-treated brain homogenates in generating the cAMP as a result of changes in numbers of the beta-receptors. Experimentally, the membrane homogenates were incubated with labeled ATP in the presence or absence of NE or isoproterenol, the formed cAMP was then measured and the adenylate activity was calculated.

Chronic administration of antidepressants have been found to down-regulate the beta-receptors in several brain regions. However, this phenomenon does not occur with all antidepressants in use today; some novel tricyclic and non-tricyclic antidepressants fail to produce this effect after chronic treatment. Thus some variability of effect on down-regulation of beta-receptors upon chronic treatments does exist.

To address this problem Surany**i**-Cadotte et al (2) had conducted experiments showing the effect of chronic treatment with different classes of antidepressants on beta-adrenergic receptors in rat brains. DMI, zimelidine and bupropion at dose of 10 mg/Kg were injected intraperitoneally twice daily for 21 days into rats. Twenty-four hours after the last dose animals were sacrificed, the brains were removed, frozen and stored at -70°C. For binding assay, crude synaptic membranes were prepared by homogenization. Pellet was resuspended in assay buffer of which aliquots were taken for incubation with ^{3}H-DHA and buffer alone or buffer together with propranolol. The incubation was terminated by rapid filtration on glass fiber filters. The radioactivity was counted. Specific binding was obtained as radioactivity bound in the presence and absence of propranolol.

The Kd and Bmax were calculated by Scatchard analysis. Results are shown below.

Treatment	Bmax (fmoles/mg protein)	Kd (nM)
Saline	82 ± 11	1.9 ± 0.5
DMI	55 ± 8*	1.9 ± 0.4
Zimelidine	63 ± 9	2.1 ± 0.5
Bupropion	67 ± 10	2.2 ± 0.4

*$P < 0.05$

Results shown indicate that only DMI significantly decreases the density of beta-receptors while there is no significant change of the affinity on binding. Therefore, it suggests that clinically effective antidepressants may display variable effect on beta-receptors or other neuronal activities may modulate this effect. Zimelidine also decreases the NE-activation of the adenylate cyclase (result not shown) without reducing the number of beta-receptors (contrast to that shown in Table 1.) further indicates that these two systems are under separate regulatory control. The fact that antidepressants act on both pre-and postsynaptic neurons even complicates the issue.

Down-regulation of beta-adrenergic receptors and serotonergic input

Recently, many investigators have begun to question the role of serotonergic input on the down-regulation of beta-adrenergic receptors by chronic treatment of antidepressants. Since several tricyclic antidepressants bind with high affinity to serotonergic axons therefore a reciprocal

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functional relationship between certain serotonergic and adrenergic axons can exist. Hence, down-regulation of the noradrenergic system elicited by repeated administrations of typical antidepressants may not be exclusively due to an action on noradrenergic neurons but may also be due to an action on serotonergic axons as well.

To test whether the serotonergic axons are involved in the down-regulation of noradrenergic receptors elicited by antidepressant drugs most experiments were designed using lesioning of specific central serotonergic neurons by 5,7-dihydroxytryptamine (5,7-DHT) before repeated administration of the antidepressants in question.

The test system usually comprises of a) lesioning of serotonergic neurons by 5,7-DHT; b) binding study; c) NE or isoproterenol-sensitive cAMP generating system study; d) verification of effectiveness of lesioning.

Rats were pretreated with DMI, i.p., 40-60 min prior to intraventricular injection of the neurotoxin as to prevent destruction of the noradrenergic neurons. Animals were allowed to recover for 7-12 days and then were injected with DMI 15-20 mg/Kg/day, i.p., for 21 days. At 24-48 hrs after the last injection of DMI the animals were decapitated and their brains were removed. Cortex was dissected and frozen (some investigators used fresh tissues for studies of cAMP response to NE or isoproterenol).

In binding studies ^{3}H-DHA was used as the ligand; non-specific binding was determined in the presence of alprenolol and was substracted from total binding to give specific binding. Incubation was terminated by

rapid filtration on glass fiber filtres, washed with cold buffer and radioactivity was determined.

The study of adrenergic-sensitive adenylate cyclase was done by using crude synaptic membrane preparations from rat cerebral cortex incubated with NE or isoproterenol and having ^{32}P-ATP as the substrate together with other essential cofactors. The amount of ^{32}P-cAMP formed was quantitated by counting its radioactivity.

The effectiveness of lesioning was also verified by measurement of 5HT and NE in the cortex. Most data showed a marked and selective reduction in the 5HT contents without affecting the contents of NE found in the same brain areas.

Results shown below are from the works of Brunello and colleagues (3) and Janowsky et al (4)

From Fig 1 and Table 2 it can be concluded that in the absence of serotonergic neuronal input, DMI failed to reduce the density of beta-adrenergic receptors without any significant changes in binding affinities in all cases.

The responsiveness of the cAMP-generating system to both NE and isoproterenol was reduced in lesioned animals (Tables 2, 3). This is in contrast to the results of Brunello's group (Fig 2). The difference may be due to the design of the experiment. In Janowsky's group animals were allowed to recover 10-12 days following lesioning, the repeated injection of DMI 15 mg/Kg daily was done for 7 days and fresh brain homogenates were used. In Brunello's group animals were allowed to recover 7 days, DMI at 20 mg/Kg daily was chronically injected for 21 days and frozen

tissues were used for assay of adenylate cyclase activity. These factors may contribute in certain extent to the difference of the results.

This apparent discrepancy clearly indicates that subsensitivity of the adenylate cyclase system is generally but not always linked to a reduction in the density of beta-receptors thereby changing in both parameters is not necessary in the same direction. It is possible that alteration of the receptor sensitivity preceeds the actual loss of the receptor sites during development of neuronal subsensitivity.

Table 2 *Effect of DHT lesions of the central serotonergic system on the recognition and action functions of the NE receptor-coupled adenylate cyclase system. The lesions were made 10 to 12 days before treatment with desipramine (15 mg/kg. intraperitoneally) daily for 7 days. Twenty-four hours after the last desipramine injection, the animals were decapitated and the cyclic AMP responses to NE and the density of β-adrenergic receptors were determined. Each response equals the stimulated concentration of cyclic AMP minus the basal level. For the determination of specific ^{3}H - DHA binding, no fewer than five different concentrations of ligand (0.3 to 3.5 nM) were used. Numbers in parentheses indicate the number of animals, each sample being analyzed in duplicate (cyclic AMP) or in triplicate (DHA binding). Values are means ± standard errors.*

Treatment	Cyclic AMP (pmole/mg protein)		^{3}H-DHA binding	
	Basal concentration	Response to 100 μM NE	Maximum number of sites (fmole/mg protein)	Affinity (nM)
No lesion; saline	18.0±2.5(10)	65.2±6.3(17)	100±10(8)	1.31±0.13
No lesion; desipramine	17.4±2.0(12)	27.0±3.6*(17)	68±4†(8)	1.32±0.07
Lesion; saline	18.1±1.3(13)	50.7±4.6(23)	131±4†(7)	1.56±0.08
Lesion; desipramine	17.7±1.7(13)	23.9±3.1+(20)	133±25(7)	1.71±0.21

*Significantly different from corresponding value for nonlesioned animals given saline (P <.001)†P <.025. + Significantly different from corresponding value for lesioned animals given saline (P <.001) (After (4)).

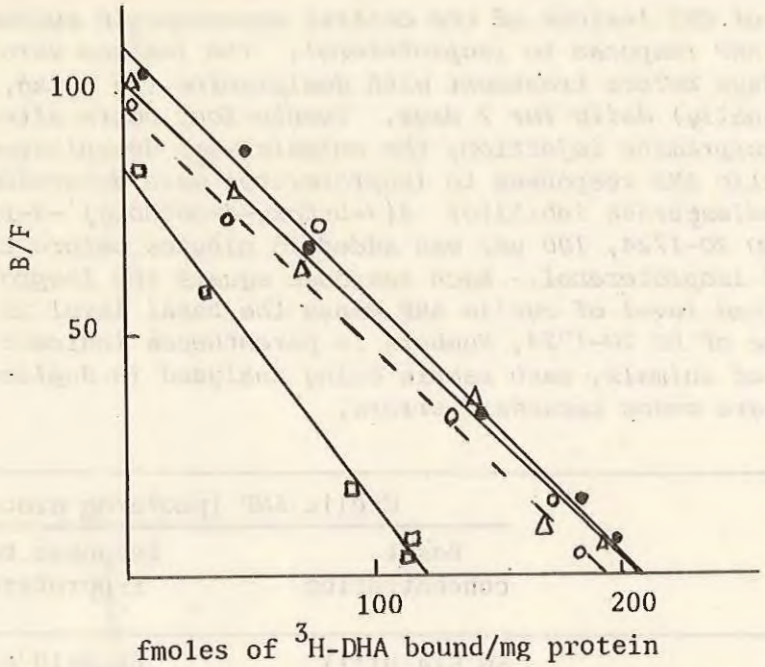

Fig. 1 *Scatchard analysis of ^{3}H-DHA binding to cortical membranes in sham-operated (control) or 5,7-HDT-lesioned rats receiving repeated injections of saline or DMI: 5,7-DHT lesion prevents the down-regulation of ^{3}H-DHA binding sites. For treatment schedule see Methods. ●——● Control, K_d 1.85 nM, Bmax = 200 fmol/mg protien; □——□ Chronic DMI, K_d 1.54 nM, Bmax = 123 fmol/mg protein; ○---○ Lesioned, K_d 1.94nM, Bmax = 195 fmol/mg protein; △——△ Lesioned + DMI K_d 2.1 nM, Bmax = 205 fmol/mg protein. (After (3)).*

Furthermore, destruction of serotonergic neurons by 5,7-DHT has eliminated the possibility that 5HT itself as well as other comodulator substances either released from or dependent on serotonergic neurons for its release may be essential for this down-regulation. Whether the serotonergic neurons or 5HT itself is essential for this mechanism is another dispute. Recently, Manier et al (5) and Racagni and Brunello (6) had shown that in rats in which 5HT contents had been depleted after chronic treatment with p-chlorophenylalanine (pCPA), chronic DMI treatment could

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Table 3 *Effect of DHT lesions of the central serotonergic system on the cyclic AMP response to isoproterenol. The lesions were made 10 to 12 days before treatment with desipramine (15 mg/kg, intraperitoneally) daily for 7 days. Twenty-four hours after the last desipramine injection, the animals were decapitated and the cyclic AMP responses to isoproterenol were determined. The phosphodiesterase inhibitor 4(3-butoxy-4-methoxy) -2-imidazolidone (RO 20-1724, 100 μM) was added 15 minutes before the addition of isoproterenol. Each response equals the isoproterenol-stimulated level of cyclic AMP minus the basal level in the presence of RO 20-1724, Numbers in parentheses indicate the number of animals, each sample being analyzed in duplicate. Values are means ±standard errors.*

Treatment	Cyclic AMP (pmole/mg protein)	
	Basal concentration	Response to 10 μM isoproterenol
No lesion; saline	50.5±4.0(11)	66.9±10.6 (12)
No lesion; desipramine	43.4±4.3(10)	39.7± 6.2*(10)
Lesion; saline	50.0±2.5(11)	62.7± 8.9 (12)
Lesion; desipramine	50.1±5.0(11)	30.0± 5.1†(10)

*Significantly different from corresponding value for nonlesioned animals given saline ($P<.001$). †Significantly different from corresponding value for lesioned animals give DHT ($P<.005$). (After (4)).

no longer produce desensitization of beta-receptors. Thus it seems that 5HT per se is important. However, Nimgaoukar et al (7) demonstrated down-regulation of beta-receptors occurred following chronic DMI treatment when 5HT was depleted by pCPA but not when the neurons were lesioned with 5,7-DHT. This discrepancy suggests another inherent factor(s) such as a cotransmitter, hormonal influences or the membrane fluidity might contribute to the variability of the responses. A cotransmitter mechanism might be operative in subsensitivity of cAMP-generating system independently of reduction in beta-receptor numbers. Two populations of adrenergic recep-

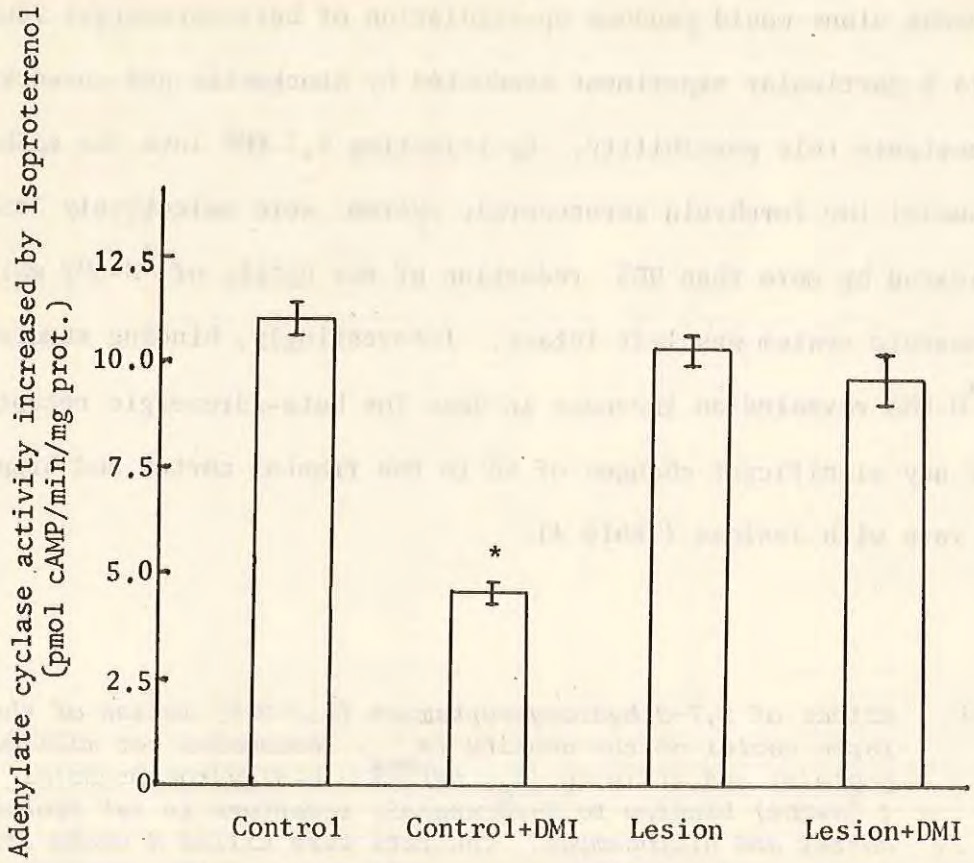

Fig. 2 *Isoproterenol-stimulated adenylate cyclase activity in membranes prepared from cortices of sham-operated or 5,7-DHT-lesioned rats, both receiving repeated injections of saline or desmethylimipramine (DMI). The basal activities (31 ± 3, 32 ± 5, 33 ± 3 and 33 ± 4 pmol/min/mg prot. in sham-operated (control), sham + DMI, 5,7-DHT-lesioned and 5,7-DHT + DMI, respectively) have been subtracted from the values obtained in the presence of 1 μM isoproterenol. *P < 0.05 in respect to sham-operated animals. (After (3)).*

tors coupled to adenylate cyclase have been described, and only one type has beta-receptor characteristic. These subpopulations of receptor may be under separate endocrine control which will result in different responses upon changing in hormonal levels.

A question then arises whether selective lesioning of serotoner-

gic neurons alone would produce up-regulation of beta-adrenergic receptors. There is a particular experiment conducted by Stockmeier and co-workers(8) to demonstrate this possibility. By injecting 5,7-DHT into the midbrain raphe nuclei the forebrain serotonergic system were selectively lesioned as indicated by more than 90% reduction of the uptake of ^{3}H-5HT while the noradrenergic system was left intact. Interestingly, binding studies using ^{3}H-DHA revealed an increase in Bmax for beta-adrenergic receptor without any significant changes of Kd in the frontal cortex and hippocampus of rats with lesions (Table 4).

Table 4 *Effect of 5,7-dihydroxytryptamine (5,7-DHT) lesion of the raphe nuclei on the density (B_{max}, femtomoles per milligram of protein) and affinity (K_d, nM) of ^{3}H-dihydroalprenolol (^{3}H-DHA) binding to β-adrenergic receptors in rat frontal cortex and hippocampus. The rats were killed 4 weeks after lesions. Values (mean ± standard error of the mean) were determined by least-squares linear regression analyses of Scatchard plots (n = 8 to 9 for frontal cortex; n = 5 for hippocampus). The hippocumpi from three rats were pooled for each analysis.*

Treatment	^{3}H-DHA binding	
	B_{max}	K_d
	Frontal cortex	
Control	154.6 ± 7.0	1.3 ± 0.1
5,7-DHT	201.6 ± 8.1*	1.6 ± 0.2
	Hippocampus	
Control	154.2 ± 9.9	6.0 ± 0.9
5,7-DHT	291.4 ±25.0*	6.4 ± 0.3

* P <0.001 compared to control. (After (8)).

Consistent with this result is the effect of systemic injection of p-chloramphetamine which selective lesioned the central serotonergic neurons also produced an increase in both binding of ^{3}H-DHA to beta-adrenergic receptors and production of cAMP in response to isoproterenol (Fig 3).

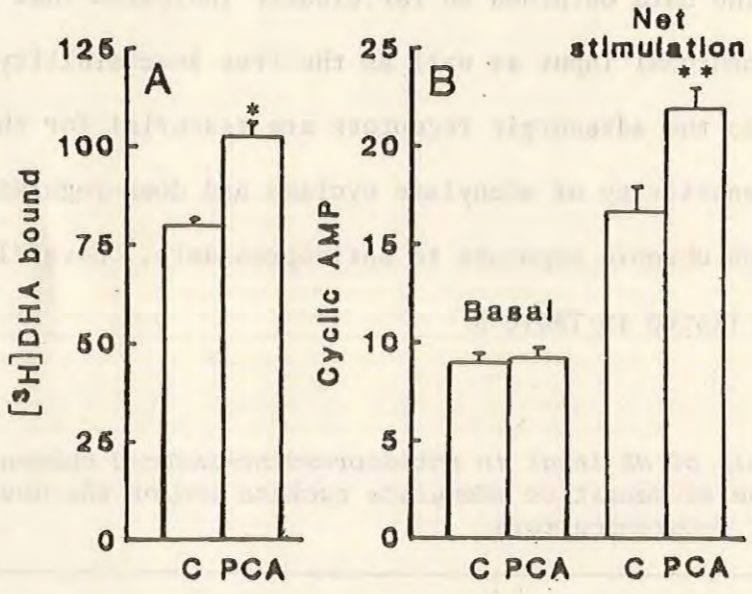

Fig. 3 *Effect of lesions of serotonin axons with p-chloramphetamine (PCA) on (A) the binding of ^{3}H-dihydroalprenolol (^{3}H-DHA, femtomoles per milligram of protein) to β-adrenergic receptors and (B) isoproterenol-stimulated production of cyclic AMP (picomoles per milligram of protein) in the hippocampus. The concentration of ^{3}H-DHA used was 5.9 nM. β-Adrenergic receptor-mediated stimulation of cyclic AMP was determined by incubating hippocampal minces with 10 μM L-isoproterenol for 10 minutes in the presence of 50 μM isobutylmethylxanthine. Net stimulation equals total cyclic AMP in the tissue after incubation with isoproterenol minus the basal level. Values represent the mean ± standard error of the mean (n = 15 to 16). (*) P < 0.001, (**) P < 0.01 compared to control (C). (After (8)).*

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Down-regulation of beta-receptor and noradrenergic input

The role of adrenergic neurons in down-regulation of beta-receptor has also been an intense investigation being conducted at present. Experimental design usually utilizes the same priciples as in studying the role of serotonergic neurons. However, some modifications do exist, 6-hydroxydopamine was usually used as a neurotoxin to lesion the noradrenergic neurons in the brain. Unilateral lesions of specific brain areas were performed. The data obtained so far clearly indicated that an intact noradrenergic neuronal input as well as the free accessibility of the neurotransmitter to the adrenergic receptors are essential for the development of both subsensitivity of adenylate cyclase and down-regulation of beta-receptors upon chronic exposure to antidepressants. Several lines of evidence are listed in Table 5

Table 5 *Role of NE input in antidepressant-induced subsensitivity of the NE-sensitive adenylate cyclase and/or the down-regulation of β-adrenoceptors*

1.	No down-regulation and/or subsensitivity if β-adrenoceptors are blocked by propranolol.
2.	No down-regulation following destruction of NE neurons by 6-hydroxydopamine.
3.	No subsensitivity to NE following lesions of the locus ceruleus.
4.	α_2 -Blockade plus DMI or MAO inhibitors intensifies and shortens onset of down-regulation of β-adrenoceptors.
5.	Clorgyline (MAO-A inhibitor) but not deprenyl (MAO-B inhibitor) causes subsensitivity to NE and down-regulation of β-adrenoceptor density.
6.	(+)-Oxaprotiline (potent NE-uptake inhibitor) but not (-)-oxaprotiline (weak NE-uptake inhibitor) causes subsensitivity to NE and down-regulation of β-adrenoceptor density.

DMI, desipramine; MAO, monoamine oxidase. (After (1)).

In conclusion, much evidence seems to support the supersensitivity of the central adrenergic receptors as being a cause of the affective disorders. However, one must be cautious when correlating these data obtained from treatment of experimental animals to that occur in humans. At present, evidence of these adaptive changes that might occur in humans is limited. Moreover, it is not certain whether down-regulation of beta-receptors is a consequence or the cause of the antidepressive actions.

There are at least three points of interest in this kind of study worth mentioning. First, all experiments so far reported utilized brains of normal rats being treated with antidepressants or neurotoxins instead of brains of depressive rats, so it would rather be difficult to extrapolate the effect of drugs to what it should be in the disease states. The diseased animals should be a better model for this type of study as is the case of spontaneous hypertensive rat (SHR) used in study the effect of antihypertensive agents. Second, more specific ligand may be necessary for binding studies since ^{3}H-DHA interacts with both high and low affinity state of adrenergic receptors. Besides this, biological effect of ^{3}H-DHA should have been demonstated. Lastly, beta-agonist drugs which both activate the beta-receptor coupled adenylate cyclase system and produce delayed down-regulation of beta-receptors should be tested for their antidepressive effect either by iontophoretically or in vivo study when the drug readily penetrates the blood brain barrier.

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