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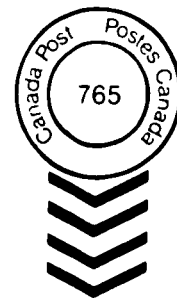
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Noradrenergic Function and Depression, Too Much or Too Little?

J.W. MAAS and Y. HUANG

SUMMARY: *Antithetical hypotheses as to CNS noradrenergic function in depressed patients can be constructed from results of pharmacological studies of the effects of antidepressant drugs. The experimental data supporting each of these opposing propositions is briefly reviewed in this paper. Finally, the results of clinical studies of noradrenergic function in depressed patients are noted and discussed in terms of these disparate hypotheses.*

RÉSUMÉ: *À partir des résultats d'études pharmacologiques de l'effet de drogues antidépression, il est possible d'émettre des hypothèses tout à fait opposées sur le rôle de la noradrénaline centrale dans la dépression. Nous présentons une revue et une analyse des données expérimentales supportant ces vues divergentes. Nous présentons enfin le résultat d'expériences cliniques chez des patients déprimés et les discutons à la lumière de ces hypothèses.*

Earlier findings which indicated that rauwolfia alkaloids, which deplete brain norepinephrine (NE), could precipitate severe depressions and that monoamine oxidase inhibitors, which raise brain NE, produced elevations in mood led to the suggestion that depressive states were associated with decrements in brain NE. This "catecholamine hypothesis" was strengthened by the finding that acute administration of an antidepressant, imipramine, resulted in a blockade of the reuptake of NE (Schildkraut, 1965; Bunney and Davis, 1965). Results of clinical studies have also been generally consistent with this hypothesis for some subtypes of depression. For example, cycling bipolar patients excrete less urinary 3-methoxy-4-hydroxyphenethylglycol (MHGP), the principal metabolite of brain NE, when depressed than when euthymic or manic; bipolar depressed patients excrete less MHGP than do normal subjects; there is a subtype of a depressed patient who is characterized by a low pretreatment MHGP, a brightening of mood after a trail of d-amphetamine, and a favorable response to treatment with imipramine or desmethylimipramine (DMI) (Maas, 1978; Van Kammen and Murphy, 1978; Cobbin et al., 1979).

Over the past several years, however, a more complete understanding has emerged regarding the mechanisms by which NE neuron functioning is regulated, and previously unknown pharmacological effects of chronically administered antidepressant drugs have been elucidated. These effects of chronic drug administration are of particular interest since it is known that therapeutic effects are generally not seen until 2 to 4 weeks after the beginning of treatment. These newer findings with chronic drug administration have led some investigators to suggest that rather than there being a

deficiency of brain NE in depression, this illness is characterized by a hypersensitivity of NE postsynaptic receptors (Sulser et al., 1978). From a functional standpoint this newer hypothesis is the direct antithesis of the earlier catecholamine hypothesis.

In this paper these more recent findings regarding the pharmacological effects of chronic treatment with imipramine or DMI will be reviewed in terms of their congruence with both the earlier and more recent hypotheses as to relationships between brain NE and depression. Finally a comment as to the implications which these more recent pharmacological data have for the interpretation of the noted clinical findings will be given.

The effects of chronic treatment with antidepressant agents may be briefly listed as follows:

1. Chronic treatment with DMI produces a decrement in brain tyrosine hydroxylase and brain NE (Segal et al., 1974; Schildkraut et al., 1970).
2. The acute effect of DMI on the blockade of reuptake of NE is also found with chronic treatment (Schildkraut et al., 1970).
3. Chronic treatment with a variety of antidepressants, including electroshock, produce a decrease in the sensitivity of postsynaptic β adrenergic receptors (Sulser et al., 1978; Banerjee et al., 1977).
4. Chronic treatment with imipramine or DMI results in a diminution in the levels of the cofactor s-adenosylmethionine (Taylor et al., 1975).
5. Chronic treatment with DMI produces a decreased sensitivity of auto receptors on presynaptic membranes and cell bodies (Crews and Smith, 1978; Wolfe et al., 1978).

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Table 1

Proposition I	Proposition II
Antidepressant drugs have the following actions and hence produce a decrease in the functional state of CNS NA systems.	Antidepressant drugs have the following actions and hence produce an increase in the functional state of CNS NA systems.
1. decrease tyrosine hydroxylase	1. increase MHPG
2. decrease endogenous brain NE content	2. block reuptake
3. decrease postsynaptic β -adrenergic receptor sensitivity	3. decrease s-adenosylmethionine
4. decrease postsynaptic β -adrenergic receptor density	4. decrease the sensitivity of α_2 autoreceptors on cell bodies and terminals
5. decrease basal firing rate of the locus coeruleus	

6. Chronic treatment with imipramine or DMI is associated with a decrease in the basal firing rate of cell bodies within the locus coeruleus (Svensson and Usdin, 1978).

From this list it is apparent that depending upon how much weight is given to each of the above, rather different views of the chronic effects of antidepressant drugs can be developed. For example, one could argue that the blockade of reuptake of NE when combined with a decreased sensitivity of the presynaptic receptors will overshadow both the drug induced decrease in postsynaptic receptor sensitivity and the decrease in the basal firing rate of the locus coeruleus. Quite obviously, the opposite type of argument could also be made. This point is made by Table 1 which lists the above findings in terms of their support for opposing propositions.

What is needed to resolve this issue is not further data dealing with drug effects on isolated portions of neurotransmitter systems, but rather information as to the effects of drugs on the integrated functioning of the NE neuron-following cell complex. For this reason, recent reports by Huang are of interest. Rats were chronically treated with DMI or iprindole and the effects upon the basal firing rates of hippocampal neurons which had a demonstrated inhibitory NE input were studied. Chronic treatment with either DMI or iprindole resulted in an increase in the basal firing rate of these

postsynaptic neurons; thus indicating that under basal conditions the integrated effect of chronic drug treatment is the production of a decrease in the overall functioning of NE systems (Huang, 1979). If similar results are found with other antidepressant agents and in other than basal conditions, a strong case can be made for Proposition I (see Table 1) rather than Proposition II being correct.

As was noted, the available clinical data as to MHPG excretion and response to imipramine and amphetamine by a subtype of depressed patients is compatible with proposition II as defined in Table 1. How are these clinical findings to be interpreted if future results are sufficiently robust to favor the acceptance of proposition I? One possible explanation is the following. A primary postsynaptic hypersensitivity of NE neuron follower cells is associated with a compensatory increase in the sensitivity of α_2 autoreceptors on cell bodies and synaptic terminals which results in a decrease in impulse flow in NE neurons and a decrement in MHPG production. This explanation would also be consistent with the mood change after imipramine or amphetamine.

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