Introduction

Norepinephrine: Neurotransmitter for the Millennium

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Although options for the pharmacologic treatment of depression have grown exponentially over the past several decades, the current armamentarium of antidepressants continues to have considerable limitations. There is no doubt that the newer antidepressants represent a quantum leap in terms of tolerability when compared with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs); however, progress toward the introduction of novel agents with improved efficacy has not been realized. This latter point, taken into consideration with the less-than-ideal side effect profile of the new antidepressants, highlights the need for new antidepressant development. The goals of antidepressant therapy are, of course, to induce complete remission and prevent relapse or recurrence. Although 70% to 80% of patients fulfill response criteria in antidepressant clinical trials, only 40% to 50% meet criteria for remission and, for multiple reasons, 50% to 80% ultimately relapse. Further analyses reveal that only 20% to 25% of depressed patients have a complete remission with their first antidepressant regardless of the drug selected. Another 30% to 45%, depending on the study and the drug, show only a partial response. Patients may go from being severely depressed to moderately depressed or from moderately depressed to mildly depressed, but they are not euthymic, i.e., not in remission. Regrettably, 25% to 35% of patients are considered nonresponders (i.e., improvement of 20% or less). Patients are clearly not exhibiting the optimal response with the current pharmacopoeia—a situation that is far from ideal.

In our battle to overcome these disappointingly low percentages of responders and remitters, we as clinicians also yearn for faster-acting antidepressants and better means of matching the psychopharmacologic profiles of the various antidepressants with individual clinical profiles to enable the selection of preferred agents and avoid the use of unsuitable ones. In this quest, we have repeatedly sought the biological basis for depression and scrutinized the role of various neurotransmitter systems in both the pathophysiology of depression and its treatment. The introduction of the selective serotonin reuptake inhibitors (SSRIs) over the last decade or so has served as a major impetus for intensive research on serotonin; consequently, relatively more is known about this neurotransmitter than virtually any others. More recently, there has been renewed interest in norepinephrine (NE)-containing circuits in the pathogenesis of depression and its treatment, particularly in severe and refractory depression. This has been, in part, stimulated by the now well-documented effects of venlafaxine and paroxetine on NE reuptake. Moreover, the recent emergence of reboxetine, the first of the selective NE reuptake inhibitors (selective NRIs), has further resulted in a reexamination of, and renewed interest in, the role of this catecholamine in the treatment of depression. During the symposium "Norepinephrine: Neurotransmitter for the Millennium," presented

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at the 1999 American Psychiatric Association meeting in Washington, D.C., speakers examined the role of the NE systems in depression. The articles that follow are based on those presentations.

Alan Frazer, Ph.D., reviews the role of NE-containing neural circuits in the pathophysiology of depression, highlighting the effects of NE on many brain regions thought to be involved in the signs and symptoms of depression. My colleague Jane F. Gumnick, M.D., and I summarize problems with currently available antidepressants. Amit Anand, M.D., and Dennis S. Charney, M.D., describe the behavioral effects of NE depletion in patients with depression. Their findings suggest that NE depletion in depressed patients is most closely associated with a decline in energy, loss of interest, decreased ability to experience pleasure, decline in motivation, and decreased concentration. Using reboxetine, the only selective NRI, as a probe for NE effects, Alan F. Schatzberg, M.D., reports the data from clinical trials of reboxetine, which show comparable or greater efficacy for reboxetine than for imipramine, desipramine, and fluoxetine and quite acceptable tolerability for reboxetine. The positive effect of reboxetine on social functioning and improvements in core depressive symptoms, especially anergia and anhedonia, without the introduction of anxiety, bode well for the antidepressant's becoming an important addition to the U.S. pharmacopoeia. For further detailed information on the role of NE systems in depression, see the recently published comprehensive review by Ressler and Nemeroff.[1]

REFERENCE

1. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biol Psychiatry 1999;46:1219–1233