Anticholinergic Mechanisms: A Forgotten Cause of the Switch Process in Bipolar Disorder

To the Editor: In their review of the neurobiology of the switch process in bipolar disorder, Salvadore et al[1] discuss such neurobiological factors as abnormalities in catecholamine levels, up-regulation of neurotrophic and neuroplastic factors, hypothalamic-pituitary-adrenal axis hyperactivity, and circadian rhythms. However, they have ignored anticholinergic enhancement as a possible factor in mood switch. Such a mechanism has long been postulated, on the basis of evidence of anticholinergic activity of tricyclic antidepressants (TCAs)[2] and within the context of a cholinergic-adrenergic hypothesis of mania and depression put forth nearly 40 years ago.[3]

There is a clear relationship between the mechanisms of the switch process and antidepressant activity and efficacy. A role of the cholinergic system in the mechanism of antidepressant action has been well documented on both the experimental and the clinical levels. In 1979, Browne[4] demonstrated that anticholinergic agents such as scopolamine are active in the behavioral despair test, which had previously been asserted to detect antidepressant activity. The results of neurobiological studies provided evidence of a central cholinergic receptor hypersensitivity in mood disorders.[5,6] A possible role of the muscarinic cholinergic receptor in mood disorders was subsequently demonstrated in molecular-genetic studies.[7,8] In 2006, the results of a randomized, placebo-controlled clinical trial conducted at the National Institute of Mental Health showed that the muscarinic cholinergic receptor antagonist scopolamine exerted an antidepressant effect in depressed patients with either major depressive disorder or bipolar disorder.[9] These results have been replicated and are reported in an article published this year.[10]

In 1991, Koszewska and Puzynski,[11] on the basis of an analysis of 869 depressed episodes, suggested an important role of the cholinergic system in the pathophysiology of mood switching: they observed switching into mania/hypomania most frequently during treatment with amitriptyline, the drug showing highest anticholinergic activity. In our recent retrospective analysis of antidepressant-induced mood conversion to mania/hypomania in patients treated from 1972–1996 in the Affective Disorder Unit, Institute of Psychiatry and Neurology, in Warsaw, Poland, we have demonstrated a significantly higher percentage of the switch in patients treated with TCAs than with non-TCA antidepressants.[12] Furthermore, within TCA drugs, the frequency of switch showed some correlation with the affinity of the drug to muscarinic receptors. The frequency of switch in our study was highest in patients who received amitriptyline (42%), the drug with a Kd (equilibrium dissociation constant for muscarinic acetycholine receptors in human brain) of about 18,[2] and lowest in those who received desipramine (18%), which has a Kd of about 198.[2]

Tricyclic antidepressants were the gold standard for the treatment of depression until the early 1990s. Both the distinct therapeutic efficacy in depression and the anticholinergic properties of these drugs have been widely acknowledged. However, their effect on the cholinergic system has been in recent years nearly exclusively linked to unfavorable somatic and cognitive side effect profiles, in contrast to the lack of such effects with new-generation antidepressants (mostly selective serotonin reuptake inhibitors). The possibility of a contribution of their anticholinergic effect to therapeutic action has barely been noticed. On the basis of the evidence described in this letter, we believe that a meaningful role of anticholinergic mechanisms operating in antidepressant activity, and consequently in switch processes, deserves to be strongly mentioned.

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