

Mania: gender, transmitter function, and response to treatment

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Abstract

Noradrenergic and GABA systems may be involved in mania, but there is little information about relationships between the function of these systems and response to specific antimanic treatments. We investigated relationships between indices of catecholamine or GABA system function, pretreatment mania severity and antimanic response to divalproex, lithium, or placebo. Plasma GABA and urinary excretion of catecholamine metabolites were measured before randomization to lithium, divalproex or placebo in patients hospitalized for manic episodes. Severity of mania was evaluated using the Manic Syndrome, Behavior and Ideation and Mania Rating Scale scores from the SADS-C. Multiple regression analysis showed that pretreatment plasma GABA was related to severity of manic symptoms. This relationship seemed stronger in women. Multiple regression analysis showed that pretreatment levels of urinary MHPG correlated with improvement in manic syndrome scores. These data suggest that GABA and norepinephrine may be related to different aspects of the manic state and to its pharmacologic sensitivity. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Bipolar disorder; Norepinephrine; MHPG; GABA; Treatment outcome; Lithium; Valproate; Placebo

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1. Introduction

Manic episodes are associated with neurotransmitter system changes that may be related to their pathophysiology and treatment response. Noradrenergic function is increased in mania (Swann et al., 1987b; Azorin et al., 1990), and returns toward normal during lithium treatment, even if mania persists (Swann et al., 1987b). Therefore, normalization of noradrenergic function is necessary but not sufficient for successful treatment of mania. Other neurotransmitters have complementary roles.

Norepinephrine–GABA interactions in regulation of sleep, attention, and activity (Singewald et al., 1995; Brancherou et al., 1996; Gervasoni et al., 1998) may be related to affective disorders (Shiah and Yatham 1998). Petty et al. (1993) suggested that low plasma GABA was a trait-related feature in episodes of bipolar disorder, possibly related to subsequent response to divalproex (Petty et al., 1996). Because antimanic treatments vary in their profiles of clinical effectiveness (Secunda et al., 1985; Swann et al., 1997), their mechanisms may differ, leading to differential relationships between treatment effectiveness and neurotransmitter function. There is, however, little information comparing pretreatment neurochemical correlates of response to antimanic agents.

Characteristics that worsen response to lithium, such as mixed states and rapid cycling, are more common in women than in men (Himmelhoch et al., 1976; Secunda et al., 1985; Coryell et al., 1992; Leibenluft 1996). Catecholamine or serotonergic function appear not to account for resistance to lithium treatment in mixed states (Swann et al., 1987b). Therefore, another transmitter may be involved, possibly in a gender-specific manner. Steroid hormones alter sensitivity to behavioral and neurochemical effects of GABA (Monteleone et al., 1988; Sundstrom et al., 1997) and norepinephrine (Schmidt et al., 1997). There is little information about the role of gender in relationships between norepinephrine or GABA and severity or treatment sensitivity of manic episodes.

We recently compared lithium, divalproex, and

placebo in the treatment of manic episodes (Bowden et al., 1994). This study reports relationships between pretreatment biological variables and (1) severity of mania and (2) change in mania ratings during 3 weeks' treatment with lithium, divalproex, or placebo. Our hypotheses were: (1) that the catecholamine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) but not GABA would be related to pretreatment mania ratings; (2) that MHPG excretion would correlate with response to lithium while plasma GABA would correlate with response to divalproex; and (3) that multiple regression analysis would reveal significant contributions to treatment response from both plasma GABA and indices of noradrenergic function.

2. Methods

2.1. General design

The design of the study has been described previously (Bowden et al., 1994; Swann et al., 1997). The study was approved by the IRBs of all participating institutions. After complete explanation of the study and informed consent, patients underwent diagnostic screening, behavior ratings and collection of samples for biological measures. Urine collections were timed from 08.00 to 11.30 h, and stored with antioxidants at -80°C until assayed (Moleman, 1985). The utility of this method has been demonstrated in psychotic patients where 24-h urine samples were not feasible (Maas et al., 1993).

Subjects were randomized to receive divalproex, lithium or placebo in a ratio of 2:1:2 (Bowden et al., 1994). Randomized treatment was continued on an inpatient basis for 3 weeks unless terminated due to recovery, deterioration, or intolerance. Ratings were repeated weekly and on the last treatment day. The SADS-C (Spitzer and Endicott, 1978) includes the Manic Syndrome Scale focusing on behavior considered diagnostic for mania including grandiosity, elevated affect, and hyperactivity; the Behavior and Ideation Scale, with items that are less specific to mania but are prominent aspects of manic episodes, and

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