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## Effects of subchronic treatment with valproate on L-5-HTP-induced cortisol responses in mania: evidence for increased central serotonergic neurotransmission

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### Abstract

The mechanisms underlying the acute and prophylactic antimanic properties of valproate have remained elusive. There are some reports that treatment with valproic acid may increase brain serotonergic neurotransmission in the rodent. This study was carried out in order to investigate the effects of subchronic therapy with valproate on central serotonin metabolism in manic patients. Toward this end, the authors examined plasma cortisol responses to 200 mg (orally) L-5-hydroxy-tryptophan (L-5-HTP) in 10 manic patients both before and after subchronic treatment with valproate. Administration of L-5-HTP resulted in significantly increased cortisol responses both before and after treatment with valproate. The L-5-HTP-induced cortisol responses were significantly higher after treatment with valproate than before treatment. It is suggested that valproate may increase central serotonergic neurotransmission and that this stimulation may play a role in the antimanic effects of valproate. © 1997 Elsevier Science Ireland Ltd.

*Keywords:* Serotonin; Valproate; Mania; Depression; L-5-Hydroxytryptophan; Cortisol

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## 1. Introduction.

Although lithium remains the treatment of choice for bipolar disorder, only 60–80% of classic bipolar patients will respond adequately (Calabrese et al., 1994). There are a number of controlled studies which have demonstrated the efficacy of carbamazepine in the treatment of bipolar disorder (Martin et al., 1994). Recent data suggest that although lithium and carbamazepine are equally effective in the acute management of refractory mania, only one third of patients on either monotherapy demonstrate moderate to marked improvement during the first 8 weeks of treatment (Small et al., 1991). These findings suggest that there are substantial numbers of bipolar patients resistant to both lithium and carbamazepine and that alternative mood stabilizers are needed. Open and controlled randomized double-blind studies evaluating the acute efficacy of valproate in manic patients suggest that valproate may be useful in the management of bipolar disorder (review: Calabrese et al., 1994).

It is thought that disorders of peripheral and cerebral  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission may play a role in the pathophysiology of mood disorders (reviews: Paredes and Agmo, 1992; Petty, 1994). Several articles have documented reduced peripheral and central GABA turnover in unipolar depressed, manic and bipolar patients (review: Maes and Calabrese, 1994; Petty, 1994) as indicated by, for example, low plasma levels of GABA; low glutamic acid decarboxylase (GAD, EC 4.1.1.15), the enzyme that synthesizes GABA from L-glutamic acid; low CSF GABA concentrations; increased GABA<sub>A</sub> receptor density in the frontal cortex of depressed suicide victims; and blunted growth hormone responses to baclofen, a GABA<sub>B</sub> receptor agonist (review: Maes and Calabrese, 1994).

There is also converging evidence that disorders in peripheral and central serotonergic activity are implicated in the pathophysiology of affective disorders (Maes and Meltzer, 1995). Major depression is accompanied by: (i) hypoactivity of central presynaptic serotonergic neurons, which is, in part, related to a lowered availability of plasma tryptophan (TRP), the precursor of sero-

tonin (5-HT); (ii) increased number, affinity or responsivity of post-synaptic 5-HT<sub>2A</sub> receptors; and (iii) downregulation of post-synaptic 5-HT<sub>1A</sub> receptors. It has been postulated that there may be an underlying deficiency in 5-HT in mania, as indicated by decreased platelet 5-HT uptake and decreased CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT (review: Meltzer et al., 1984). Interestingly, there are several reports showing a functional and anatomic association between GABA-ergic and serotonergic neurons in the brain (review: Maes and Calabrese, 1994). There is some evidence that GABA and 5-HT may coexist in some neurons (e.g. dorsal raphe) (Harandi et al., 1987; Belin et al., 1991) and that there are complex influences of GABA-ergic neurons on central serotonergic neurotransmission (Nishikawa and Scatton, 1985; Nishikawa et al., 1989; review: Maes and Calabrese, 1994).

There are also data suggesting that valproate enhances central serotonin (5-HT) synthesis and turnover. For example, acute injection of valproate may increase the turnover of 5-HT in the hippocampus and other brain regions as well (Hwang and van Woert, 1979; Kempf et al., 1982; Whitton et al., 1983, 1985; Whitton and Fowler, 1991; Biggs et al., 1992). Therefore, an interesting hypothesis is that both low GABA and low 5-HT activity predispose to affective disorders and that valproate — by increasing GABA-ergic and serotonergic neurotransmission — may compensate for these deficiencies (Maes and Calabrese, 1994). However, to the best of our knowledge, no research has examined the effects of treatment with valproate on central serotonergic activity in manic patients.

The serotonergic effects of mood stabilizers or antidepressants *in vivo* can be evaluated by measuring hypothalamic–pituitary–adrenal (HPA)-axis hormone responses, e.g. cortisol, to acute administration of L-5-hydroxytryptophan (L-5-HTP) (Meltzer et al., 1984; Maes et al., 1987, 1995). L-5-HTP causes a marked enhancement of corticosterone secretion in the blood of rats, while 200 mg L-5-HTP, in non-enteric coated tablets, reliably stimulates HPA-axis hormone secretion in humans (reviews: Fuller, 1992; Meltzer and

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