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.

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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 well as peripheral GABA receptor density in the frontal cortex of depressed suicide victims; and blunted growth hormone responses to baclofen, a GABA \(_B\) 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 (Maj et al. and Meltzer, 1995). Major depression is accompanied by: (i) hypoactivity of central presynaptic serotonin neurons, which is, in part, related to a lowered availability of plasma tryptophan (TRP), the precursor of serotonin (5-HT); (ii) increased number, affinity or responsivity of post-synaptic 5-HT\(_{2A}\) receptors; and (iii) downregulation of post-synaptic 5-HT\(_{1A}\) 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 (Harrandi et al., 1987; Belin et al., 1991) and that there are complex influences of GABA-ergic neurons on central serotonin 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 (Wang 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 (Maj and Calabrese, 1994). However, to the best of our knowledge, no research has examined the effects of treatment with valproate on central serotoninergic 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 \( \text{L-} \)5-hydroxytryptophan (\( \text{L-} \)5-HTP) (Meltzer et al., 1984; Maes et al., 1987, 1995). \( \text{L-} \)5-HTP causes a marked enhancement of corticosterone secretion in the blood of rats, while 200 mg \( \text{L-} \)5-HTP, in non-enteric coated tablets, reliably stimulates HPA-axis hormone secretion in humans (reviews: Fuller, 1992; Meltzer and...
There is evidence that the increase in plasma cortisol following L-5-HTP in rodents and humans is modulated by at least three different post-synaptic serotonergic receptors, i.e. 5-HT₁A, 5-HT₂A and/or 5-HT₃₆ receptors (for review, see Meltzer and Maes, 1994). Significantly increased 5-HT precursor (L-TRP or L-5-HTP)-induced cortisol responses have been reported to occur in major depression (Meltzer et al., 1984; Maes et al., 1987, 1995) and mania (Meltzer et al., 1984). It is suggested that the greater L-5-HTP-induced cortisol responses in depression and mania may be attributed to an upregulation or hyperresponsiveness of post-synaptic 5-HT₂A receptors (Meltzer et al., 1984; Maes and Meltzer, 1995).

This study has been carried out in order to examine the effects of valproate treatment on central 5-HT turnover in manic patients. Toward this end, we have examined the L-5-HTP-induced cortisol responses both before and after subchronic treatment with valproate in manic patients.


2.1. Subjects.

Ten manic patients participated in this study. They were admitted to the inpatient unit of the Department of Psychiatry, Case Western Reserve University, Cleveland, OH. Diagnoses were made with the aid of the Research Diagnostic Criteria (RDC) (Endicott and Spitzer, 1978) using the Schedule for Affective Disorders and Schizophrenia (SADS) interview and extensive past history. Written informed consent was obtained from each patient. The mean age (+ S.D.) of the patients was 40.6 ± 13.5 years. There were 8 females and 2 males. The median number of previous manic and depressive episodes was 22 (range: 4–too numerous to count) and 17 (range: 5–too numerous to count), respectively. All subjects were classified as bipolar I patients, except one who suffered from schizoaffective disorder.

Severity of mania was evaluated by means of a ‘mania’ subscale (MSS), which was extracted from the SADS, i.e. the sum of the following items: elevated mood; less sleep; more energetic, efficient thinking; grandiosity; future plans; racing thoughts; extreme health; accelerated speech; motor hyperactivity; high activity; and irritability. Only subjects with a definite manic episode according to RDC and with an MSS-score > 22 were included in this study. Patients with Axis I diagnoses besides mania were excluded from this study, e.g. schizophrenia, organic mental disorders, substance abuse disorders and depression. All manic patients underwent a wash-out period of all psychotropic drugs for at least 7 days before the first placebo and L-5-HTP studies were carried out. The psychotropic drugs which patients had been taking in the weeks prior to the 7-day wash-out period were lithium (n = 2), lithium monotherapy (n = 1), lithium + haloperidol (n = 1), alprazolam (n = 1) and lithium + clonazepam (n = 1). Four patients were free of any psychotropic drugs for at least 1 month prior to these studies. All patients had normal clinical investigations, i.e. radiograph of heart and lungs, ECG, EEG and blood determinations (sedimentation rate, serum electrolytes, renal and liver function tests, thyroxine, triiodothyronine, basal thyroid stimulating hormone).

2.2. Procedures.

Each patient was tested on four occasions, i.e. placebo and L-5-HTP challenge before valproate treatment, and placebo and L-5-HTP challenge 3 weeks after subchronic treatment with valproate. A placebo condition was included in order to control for Type I and Type II errors of inference and to control for the influence of confounding variables, such as specific stress effects, memory effects, and variations in basal hormone levels (Thompson et al., 1994). The first probes were carried out at least 7 days after admission of the patients into hospital. Placebo and L-5-HTP (200 mg in non-enteric coated tablets) were adminis-
tered on 2 consecutive study days. The SADS, including the MSS, interview was carried out on the first test day. Hereafter, therapy with valproate was started. Three weeks later (21.4 ± 3.8 days), placebo and L-5-HTP probes were carried out. On the same day, raters completed the MSS.

A heparin lock catheter was inserted in the arm of manic patients at 08:30 h i.e. 60 min from baseline. Blood was drawn every 30 min from 09:00 h (T₀) until 3 h later for assay of cortisol. Either L-5-HTP or indistinguishable placebo was given immediately after catheter placement. All subjects remained supine during the test period, and they were not allowed to sleep, eat or smoke. Plasma was stored at −20°C until thawed for cortisol assay.

Cortisol was assayed by means of a radioimmunoassay; kits were purchased from Diagnostic Product Corporation, Los Angeles, CA. The analytical intra-assay coefficient of variation (CV) was 3.0% and the analytical inter-assay CV was 4.3% (mean = 13.3 μg/dl, n = 13). The cortisol secretion pattern from 09:00 to 12:00 h was computed as the area under the concentration × time course curve labeled as cortisol AUC 180. L-5-HTP was assayed on the pooled plasma samples (from T₀ until 3 h later) both before and after treatment with valproate. L-5-HTP was assayed by means of HPLC (with electrochemical detection). The inter-assay CV was < 10%.

2.3. Statistics.

The cortisol responses to placebo and L-5-HTP before and after valproate treatment were assessed by means of repeated measures analysis of variance (ANOVA) or covariance (ANCOVA) and repeated measures multivariate ANOVA (MANOVA). The effects of valproate treatment on the L-5-HTP-induced cortisol responses were evaluated in two different ways. (1) Repeated measures ANCOVA with AUC cortisol as dependent variable and baseline cortisol (T₀) as covariate. T₀ cortisol was introduced as a covariate in order to control for possible differences in basal cortisol values between the four conditions (Thompson et al., 1994). (2) Repeated measures MANOVA performed on the baseline-adjusted cortisol values (T₀ subtracted) with valproate treatment, placebo/L-5-HTP challenge and time as repeated measures. In both types of analyses, the interaction pattern of valproate treatment × placebo/L-5-HTP was the primary focus of interest since this term indicates the effects of valproate treatment on L-5-HTP-induced cortisol concentrations. The changes in the MSS and L-5-HTP-induced AUC cortisol from baseline to 3 weeks later were expressed as the Δ responses, i.e. the pre-minus post-treatment values. Wilcoxon’s paired t-test was used to compare the MSS scores and plasma L-5-HTP concentrations both before and after valproate treatment. Relationships between variables were assessed by means of Spearman’s rank order correlation coefficients.

3. Results.

Table 1 lists the cortisol AUC 180 values following placebo and L-5-HTP administration in the 10 manic patients both before and after valproate treatment. Fig. 1 shows the concentration × time curves of the post-placebo and post-L-5-HTP cortisol values in 10 manic patients before and after valproate treatment. The mean (±S.D.) dose of valproate during these neuroendocrine studies was 1400 (±592) mg daily. ANOVA showed no significant differences in basal cortisol between the placebo and L-5-HTP study days (F = 0.2, d.f. = 1,9, P = 0.6). Repeated measures design ANCOVA (with cortisol AUC 180 as dependent variable and T₀ cortisol as covariate) showed a significant stimulatory effect of L-5-HTP administration on cortisol secretion and a significant L-5-HTP × valproate treatment interaction pattern. This analysis did not show a significant effect of valproate treatment on plasma cortisol values. There was a highly significant and positive correlation between the pre- and post-treatment AUC cortisol responses to L-5-HTP (r = 0.77, P = 0.009).

Baseline-adjusted repeated measures MANOVA showed a significant effect of L-5-HTP administration (F = 23, d.f. = 1,9, P = 0.001); a significant interaction pattern between time and
Table 1
Effects of L-5-HTP administration on $T_c$ cortisol and area under the curve (A.U.C) cortisol in 10 manic patients both before and after treatment with valproate.

<table>
<thead>
<tr>
<th>Treatment with valproate</th>
<th>$T_c$ cortisol ($\mu$g/dl)</th>
<th>A.U.C cortisol ($\mu$g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo day</td>
<td>L-5-HTP</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.5 (4.6)</td>
<td>9.7 (6.0)</td>
</tr>
<tr>
<td>Post-valproate</td>
<td>10.6 (5.5)</td>
<td>10.2 (4.0)</td>
</tr>
<tr>
<td>L-5-HTP</td>
<td>$F = 1.9\ (P = 0.2)^*$</td>
<td>$F = 0.01\ (P = 0.9)^{**}$</td>
</tr>
<tr>
<td>Valproate X L-5-HTP</td>
<td>$F = 30.3\ (P = 0.0004)^{**}$</td>
<td>$F = 11.5\ (P = 0.009)^{**}$</td>
</tr>
<tr>
<td>$T_c$ cortisol</td>
<td>$F = 5.30\ (P = 0.051)^{**}$</td>
<td></td>
</tr>
</tbody>
</table>

All results are expressed as mean ($\pm$ S.D.).

* Results $P$ a NOVA on $T_c$ cortisol (d.f. = 1.9).

** Results of repeated measures ANCOVA with A.U.C cortisol as dependent variable and $T_c$ cortisol as covariate (all d.f. = 1.8).

placebo/L-5-HTP administration ($F = 28$, d.f. = 6.4, $P = 0.003$); a significant interaction pattern between valproate treatment and L-5-HTP/placebo administration ($F = 8.4$, d.f. = 1.9, $P = 0.02$); but no significant time X valproate X L-5-HTP interaction ($F = 0.6$, d.f. = 6.4, $P = 0.7$). No significant effect of valproate on cortisol values was found ($F = 0.44$, d.f. = 1.9, $P = 0.5$).

By means of Wilcoxon’s paired t-test, no significant differences could be found in plasma L-5-HTP concentrations either before (mean = $173 \pm 93$ ng/ml) or after (mean = $189 \pm 153$ ng/ml).

Fig. 1. Cortisol responses to L-5-HTP in manic patients before and after treatment with valproate (VALPR). L-5-HTP or placebo were administered at $T_c$. The measurements are shown as mean with SEM.
ng/ml) subchronic treatment with valproate. By means of Spearman’s rank order correlation coefficients, no significant correlation was found between the pre- and post-treatment L-5-HTP-induced AUC cortisol responses and plasma L-5-HTP concentrations ($r = 0.36, P = 0.14, n = 18$). By means of Wilcoxon’s matched-pairs signed-rank test, it was found that the mean MSS after valproate treatment ($19.0 \pm 7.2$) was significantly lower ($P < 0.01$) than the baseline MSS (mean $= 31.0 \pm 5.3$). By means of Spearman’s correlation analysis, no significant relationships could be found between the post-treatment L-5-HTP-induced AUC cortisol responses and the post-treatment MSS ($r = -0.07, P = 0.9$). There was no significant correlation between the $\Delta$AUC cortisol responses following L-5-HTP and the $\Delta$MSS values ($r = -0.12, P = 0.7$).

By means of Spearman’s rank order correlation coefficients, no significant relationships were found between the dosage of valproate and the post-treatment MSS ($r = 0.25, P = 0.5$) or $\Delta$MSS ($r = -0.02, P = 0.9$). There were no significant correlations between the $\Delta$AUC cortisol responses to L-5-HTP and either the dose of valproate ($r = 0.11, P = 0.8$) or the duration of treatment with valproate ($r = 0.56, P = 0.09$).

4. Discussion

The major finding of this study is that treatment with valproate for 3 weeks significantly increased the L-5-HTP-induced cortisol responses in 10 manic patients. Since the cortisol responses to acute administration of L-5-HTP are mediated, at least in part, by central 5-HT mechanisms (Maes and Meltzer, 1995), it may be suggested that subchronic treatment with valproate may stimulate central 5-HT neurotransmission in patients with mania.

These results are in accordance with previous reports showing effects of valproate treatment on serotonergic neurotransmission in rodents and humans. (i) It has been reported that treatment with valproate increases the brain concentration of 5-HIAA in whole brain or selected areas, such as striatum and tegmentum, of rodents (Horton et al., 1977; Hwang and van Wier, 1979; MacMillan, 1979; Shukla, 1985; Whitton et al., 1985; MacMillan et al., 1987; Mitsikostas et al., 1993) increased the L-5-HTP-induced cortisol responses and plasma L-5-HTP concentrations ($r = 0.36, P = 0.14, n = 18$).

Fahn (1978) reported that CSF 5-HIAA concentrations were increased after treatment with valproate in patients suffering from post-anoxic myoclonus. It has been suggested that these effects reflect a valproate-induced inhibition of the active transport of 5-HIAA out of the brain (Horton et al., 1977; Cotariu et al., 1990). Experiments with probenecid suggest that valproate acts at the same site to block the clearance of 5-HIAA out of the brain (Horton et al., 1977; MacMillan et al., 1987). (ii) Takebayashi et al. (1995) observed that the accumulation of 5-HTP, which reflects activity of tryptophan hydroxylase, in mouse cerebral cortex was not significantly altered following treatment with valproate. MacMillan (1979) could not detect changes in 5-HTP concentrations following treatment with valproate in CSF. However, valproate-treated mice showed an increased in situ activity of tryptophan-hydroxylase (Vriend and Alexiuk, 1996). These results suggest that the increase in brain 5-HIAA concentrations is at least in part related to increased 5-HT synthesis and intracellular metabolism (Vriend and Alexiuk, 1996). (iii) There are also reports which suggest significant effects of valproate on brain 5-HT concentrations. Some authors (Whitton et al., 1985; Biggs et al., 1992; Vriend and Alexiuk, 1996), but not all (Horton et al., 1977; Hwang and van Wier, 1979) found a modest increase in cerebral 5-HT concentrations in rodents following valproate treatment. In rats treated with an MAO inhibitor, valproate was found to increase whole-brain 5-HT concentrations (Whitton et al., 1983). Valproate increases extracellular 5-HT concentrations in the rat hippocampus (Whitton and Fowler, 1991; Biggs et al., 1992). (iv) There are many reports on increased tryptophan concentrations in the CNS of rodents following treatment with valproate (Horton et al., 1977; Hwang and van Wier, 1979; MacMillan, 1979; Shukla, 1985). Valproate decreases total serum tryptophan, but increases serum free and brain tryptophan concentrations, and, consequently, brain 5-HT turnover (Hwang and van Wier, 1979). Sodium valproate competitively inhibits the L-tryptophan binding to human...
serum albumin even within therapeutic concentrations of the drug (Hiraoka et al., 1992). Thus, the valproate-mediated increase in brain 5-HT may be associated to competition of the drug with tryptophan for binding sites on serum albumin (MacM illan, 1979). Our laboratory did not find any significant effects of 3 weeks of treatment with valproate (100, 200, or 400 mg/kg, intraperitoneally) on 5-HT1A or 5-HT2A receptor binding or functioning in rat brain (Khaitan et al., 1994). Pranzatelli (1988) was unable to detect direct actions of acute valproate administration at 5-HT1 and 5-HT2 receptors in adult rat brainstem.

The above results indicate that acute and subchronic treatment with valproate may increase the synthesis, release and turnover of central 5-HT, which, consequently, may lead to an enhancement of 5-HT neurotransmission. These effects of valproate appear to be partly related to increased 5-HT synthesis, which may be induced by increased availability of plasma and brain tryptophan for 5-HT synthesis and increased tryptophan-hydroxylase activity. Effects of valproate on some post-synaptic receptor subtypes other than the 5-HT1A and 5-HT2A$, such as the 5-HT2C and 5-HT3 receptors, cannot be excluded.

It was found that valproate treatment resulted in a marked clinical response in four out of the 10 manic patients (i.e. Mania Subscore $<50\%$ of baseline). In another four patients, a moderate response was observed (25–49% of baseline), and in two subjects no effect of valproate treatment could be found. There was, however, no significant relationship between L-5-HTP-induced cortisol responses and the changes in the Mania Subscale during treatment with valproate. Therefore, the present study does not offer firm evidence for the hypothesis that the efficacy of valproate in the treatment of acute mania is related to its capacity to increase brain 5-HT turnover. 'Serotonergic' antidepressants such as fluoxetine, zimelidine, clomipramine, or citalopram were shown to potentiate the L-5-HTP-induced prolactin or corticosterone secretion in rodents and cortisol in depressed patients (Lahti and Barsuhn, 1980; Maes and Eltz, 1995; Eltz et al., 1997). Thus, it appears that enhancement of central 5-HT mechanisms is common to antimanic and antidepressant treatments. Therefore, it may be suggested that 5-HT augmentation in mania, e.g. by valproate, or in depression, e.g. by some tricyclic agents or selective 5-HT reuptake inhibitors (SSRIs), restores a low 5-HT activity, which may predispose to both conditions (Maes and Calabrese, 1994). There are some other arguments which may indicate the involvement of central serotonergic pathways in the treatment of mania. First, administration of L-TRP to acutely manic patients has shown clinical efficacy in some but not all studies (Urph et al., 1974; Prange et al., 1974; Chambers and Naylor, 1978; review: van Praag and Lems, 1986). Second, lithium appears to augment 5-HT neurotransmission by enhancing the release of endogenous 5-HT in the brain (Treiser et al., 1981; Sharp et al., 1991; McCance-Katz and Katz et al., 1992). On the other hand, there are numerous reports of mania following treatment with tricyclic antidepressants, while SSRIs may be associated with fewer cases of switches to mania (review: M. Montgomery, 1995). While these results indicate that 5-HT stimulation can trigger a (hypo-) manic response, they do not allow us to conclude that 5-HT itself is the cause of mania. In this respect, it has been postulated that manic switches may be associated with altered concentrations of 3-methoxy-4-hydroxyphenylglycol, the metabolite of noradrenaline (review: Montgomery, 1995). Therefore, it could be hypothesized that a manic switch reflects changes in the equilibrium between other neurotransmitter systems, such as between 5-HT and catecholamines.

Valproate may also have a GABA-ergic mechanism of action, while disorders in central GABA-ergic transmission may play a role in the pathophysiology of affective disorders. There is some evidence that valproate may enhance GABA-ergic neurotransmission through different mechanisms, e.g. by increasing brain GABA concentrations and the release of GABA from nerve terminals (Johnston, 1984; M. M. et al., 1984; M. M. and M. Eltz, 1989; Concas et al., 1991; Keck et al., 1994). Vriend and Alexiuk (1996) reported that anticonvulsing doses of valproate significantly elevate GABA concentrations in the striatum. Chronic valproate treatment, but also chronic treatment with lithium and carbamazepine, may significantly
increase GABA \(_\beta\) receptor binding in the hippocampus (Motohashi, 1992). Thus, one common action of mood stabilizers may be mediated by GABA \(_\beta\) receptors in the hippocampus. Moreover, GABA agonists, such as progabide and fengabine, have antidepressant and anantimanic properties (review: Maes and Calabrese, 1994). There is now some evidence that GABA and 5-HT may coexist in some neurons, e.g. in the dorsal raphe (Harandi et al., 1987; Belin et al., 1991) and that there is a GABAergic control of the activity of 5-HT neurons (Harandi et al., 1987). Most importantly, systemically applied baclofen, a GABA \(_\beta\) receptor agonist, may facilitate in vivo 5-HT synthesis via primarily stimulating GABA \(_\beta\) receptors in some brain areas (Nishikawa et al., 1989). Therefore, one hypothesis is that valproate restores low GABA and low 5-HT activity in affective disorders, and that this mechanism is related to its efficacy (Maes and Calabrese, 1994).

The present study was unable to detect significant differences in plasma \(L\)-5-HTP concentrations both before and after treatment with valproate, suggesting that treatment with valproate had no significant effect on the plasma concentrations of \(L\)-5-HT following acute, oral administration. Thus, the increased cortisol responses to oral \(L\)-5-HTP administration measured after treatment with valproate are not due to pharmacokinetic interactions between valproate and the test substance. One of the limitations of the present study is that only manic patients were included. It would be of interest to examine the effects of repeated administration of valproate on \(L\)-5-HTP-induced cortisol responses in patients with major depression, epilepsy and even normal volunteers to evaluate the effects of valproate on brain serotonergic metabolism in these conditions.

In conclusion, this study showed that valproate treatment for 3 weeks significantly increased the \(L\)-5-HTP-induced cortisol responses in manic patients. These findings suggest that valproate treatment may increase serotonergic neurotransmission in the brain of manic patients. It is hypothesized that the antimanic effects of valproate may be related to its capacity to enhance both GABA-ergic and serotonergic transmission.

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References


