

# Divalproex Sodium Attenuates Growth Hormone Response to Baclofen in Healthy Human Males

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*The effect of divalproex sodium (DVP) on  $\gamma$ -aminobutyric acid-B (GABA<sub>B</sub>) receptor function in humans was assessed by measuring growth hormone (GH) responses to a challenge with a GABA<sub>B</sub> receptor agonist, baclofen, in 10 male healthy volunteers. Each subject received 20 mg of baclofen at 10:00 A.M., and blood samples were collected for measuring GH before and 30, 60, 90, 120, 150, 180 min after baclofen administration. The baclofen challenge test was repeated after 1 week of treatment with DVP (1000 mg/*

*day). The results showed that the plasma GH response to baclofen was significantly attenuated by the DVP treatment and that the degree of attenuation was positively correlated with the blood levels of valproic acid. Our findings suggest that DVP downregulates hypothalamic GABA<sub>B</sub> receptor function in humans. [Neuropsychopharmacology 18:370–376, 1998] © 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

**KEY WORDS:** *Divalproex sodium; GABA; GABA<sub>B</sub> receptor; Baclofen; Growth hormone*

Divalproex sodium (DVP) is an anticonvulsant that contains valproic acid and sodium valproate in a one-to-one molar ratio. This medication has recently been shown to be effective in treatment of acute mania (Bowden et al. 1994) and depression (Davis et al. 1996a), suggesting that, like lithium, it has antimanic and antidepressant properties. Although the mechanisms underlying the therapeutic effect of DVP in mood disorders have not been elucidated, the increase in  $\gamma$ -aminobutyric acid (GABA) levels in brain is the most often cited mechanism of action for the anticonvulsant activity of DVP (for a review, see Maes and Calabrese 1994).

GABA is the main inhibitory neurotransmitter in the mammalian brain, and GABAergic transmission modulates a variety of other neurotransmitter and neuropeptide systems (Lloyd et al. 1989; Miller and Ferrendelli 1990). This neurotransmitter acts on two main receptors in the brain, GABA<sub>A</sub> and GABA<sub>B</sub> (Hill and Bowery 1981; Matsumoto 1989). In the past decade, some evidence has accumulated, implicating a role for GABA<sub>B</sub> receptors in the pathophysiology of mood disorders and in the mechanism of action of antidepressants and mood stabilizers. In animal studies, for instance, a decrease in cortical GABA<sub>B</sub> binding has been shown in the animal models of depression such as the helpless rats and the olfactory bulbectomized rats (Lloyd and Morselli 1987). Chronic administration of tricyclic antidepressants (TCAs) normalizes cortical GABA<sub>B</sub> receptor density in both helpless (Martin et al. 1989) and bulbectomized (Joly et al. 1987) rats. Furthermore, chronic administration of antidepressants, including TCAs, monoamine oxidase inhibitors (MAO-Is), selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants, mood stabilizers such as lithium, carbamazepine,

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valproate, and electroconvulsive shock (ECS), has been reported to increase GABA<sub>B</sub> receptors in rat cortex or hippocampus (Lloyd et al. 1985; Lloyd and Pichat 1987; Szekely et al. 1987; Motohashi et al. 1989; Motohashi 1992; Pratt and Bowery 1993). Several other studies, however, were unable to confirm upregulation of GABA<sub>B</sub> receptors in the rat frontal cortex after antidepressant treatments (Cross and Horton 1987, 1988; McManus and Greenshaw 1991; Engelbrecht et al. 1994).

In humans, one way to assess GABA<sub>B</sub> receptor function is to measure growth hormone (GH) release after administration of baclofen, a  $\beta$ -p-chlorophenyl derivative of GABA and a GABA<sub>B</sub> receptor agonist (Muller 1987). This endocrine challenge paradigm is based on two observations: (1) that hypothalamic GABA<sub>B</sub> receptor sites are involved in the modulation of GH secretion (Gamse et al. 1980; Muller 1987), and (2) that the administration of baclofen induces a significant increase in GH concentrations in normal healthy humans (Koulu et al. 1979). Using this paradigm, two out of three studies (Marchesi et al. 1991; O'Flynn and Dinan 1993; Monteleone et al. 1990a) demonstrated a significant reduction of GH response to baclofen in patients with major depression compared with matched healthy controls, supporting the idea that downregulated GABA<sub>B</sub> receptor function is associated with depression. To our knowledge, there is no study to date that examined the GABA<sub>B</sub> receptor function in manic patients. Similarly, no studies to date examine the effect of DVP on GABA<sub>B</sub> receptors in humans. The purpose of this study, therefore, was to examine the effect of DVP on the GABA<sub>B</sub> receptor function in humans by measuring GH release to baclofen challenge in 10 male healthy volunteers before and after 1 week of DVP treatment.

## METHODS

### Subjects

Ten male healthy volunteers (mean age  $\pm$  SD: 25.9  $\pm$  5.8 years) gave written informed consent for participation in the study, which had been approved by the Clinical Research Ethics Committee of the University of British Columbia. Subjects were evaluated with the Structured Clinical Interview for DSM-III-R non-patient version (SCID-NP; Spitzer et al. 1992), a medical history and a physical examination by a research psychiatrist. All subjects had no past or present psychiatric history and had no current medical conditions. They were free of a family history of psychiatric illness in first-degree relatives. They were also medication-free for a minimum of 4 weeks prior to study, smoked fewer than five cigarettes per day, and ingested no more than the equivalent of five beers per week and three cups of coffee per day.

### Procedures

Subjects, having fasted from midnight, reported to the research unit between 8:00 A.M. and 8:30 A.M. on the day of the baclofen test. After being weighed (mean weight  $\pm$  SD: 79.0  $\pm$  14.5 kg), they reclined on a bed in a comfortable position with the head elevated. An intravenous cannula was inserted in a forearm vein at 8:30 A.M., and subjects were allowed to rest but not to sleep, smoke, or eat. The first blood sample for baseline GH level was taken at 10:00 A.M. (time "0"). Baclofen 20 mg was given orally at this time, and further blood samples were collected every 30 min for 3 h (six samples). Subjects also rated at baseline, 60, 120, 180 min on 100 mm visual analogue scales (VAS; 0 = not at all, 100 = most ever) on four subjective states (nausea, drowsiness, headache, concentration). Pulse rate and blood pressure were recorded at regular intervals throughout the procedure.

After the pretreatment study, subjects received DVP 1,000 mg/day (500 mg in the morning and 500 mg in the evening) for 7 consecutive days on an outpatient basis. During the 7 days, subjects were asked to record the side effects of DVP with an open questionnaire. The side effects reported in the questionnaire were classified as mild, moderate, and severe, and were defined by "not affecting usual activity," "mild disruption in usual activity," and "major disruption in usual activity," respectively. Subjects took the last dose of DVP at 10:00 P.M. on the 7th day, and baclofen challenge was repeated at 8:30 A.M. of the 8th day. An additional blood sample was taken at 10:00 A.M. (12 h after the final dose) on the day of testing for measuring the blood levels of valproic acid to check for compliance (mean valproic acid level  $\pm$  SD: 513.8  $\pm$  92.4  $\mu$ mol/L). Dose and drug administration as well as hormonal and behavioral monitoring were identical to those in the pretreatment study.

### Biochemical Assays

Venous samples were collected into tubes containing EDTA, stored on ice, and centrifuged within 60 min. Serum was separated and then was stored at  $-80^{\circ}\text{C}$  for assay at a later time. All samples from each subject were assayed in the same batch. The samples were assayed by a lab technician blind to the study conditions. Valproic acid concentrations were determined using Fluorescence Polarization Immunoassay (FPIA), GH was assayed by Quantitope HGH Radioimmunoassay (Kallestad diagnostics). The sensitivity of GH assay was 0.2 ng/ml. The interassay coefficients of variation were 10.8% for GH pool of 2.6 ng/ml, 6.6% for GH pool of 5.8 ng/ml, and 5.7% for GH pool of 11.3 ng/ml. The intraassay coefficients for GH were 6.8%, 5%, and 9.1% for GH pools of 2.5 ng/ml, 5.4 ng/ml, and 35.2 ng/ml, respectively.

## Statistics

Wilcoxon signed-rank test was used to compare the baseline GH levels between pre- and posttreatment conditions, because the GH data were not normally distributed. Repeated measures analysis of variance (ANOVA) was used to examine the treatment effect of DVP on the GH responses to baclofen, which were measured as the net change from baseline at each time point after challenge (labeled as  $\Delta$  GH). Post hoc comparisons were carried out using Wilcoxon signed-rank tests. The GH responses were also calculated as (1) the net maximal response (labeled as  $\Delta_{\max}$  GH), that is, the peak response minus baseline, and (2) the net area under the time curve (labeled as AUC GH), using trapezoidal method with subtraction of the baseline values. The change in  $\Delta_{\max}$  GH was defined by the difference between pretreatment  $\Delta_{\max}$  GH and posttreatment  $\Delta_{\max}$  GH. Behavioral responses to baclofen (labeled as  $\Delta_{\max}$  VAS scores) were calculated as the difference between baseline VAS scores and maximal peak scores. The  $\Delta_{\max}$  and AUC GH data as well as  $\Delta_{\max}$  VAS scores were analyzed with Wilcoxon signed-rank tests. Relationships between variables were assessed by means of Spearman's rank order correlation coefficients. All significance levels reported were two-tailed. Data were reported as mean  $\pm$  SD. The data were analyzed using the Statistical Package for Social Sciences (SPSS) software.

## RESULTS

The data for baseline, peak,  $\Delta_{\max}$ , and AUC GH of the 10 subjects are presented in Table 1. Two out of the 10 sub-

jects were excluded from data analysis. One subject did not have an increase in GH response to baclofen challenge before DVP treatment (defined by  $\Delta_{\max}$  GH  $> 0.5$  ng/ml, Davis et al. 1996b), and the other one had baseline GH levels above 5  $\mu$ g/L post-treatment. The exclusion of subjects with large baseline GH levels is standard practice because after a GH secretory episode, the pituitary is relatively refractory (Vance et al. 1985). For the remaining eight subjects, there was no significant difference in baseline plasma GH levels between pretreatment and posttreatment conditions ( $0.56 \pm 0.32$  vs.  $0.98 \pm 0.70$  ng/ml;  $Z = -1.54$ ,  $p = .12$ ). The baclofen-induced GH response measured as  $\Delta_{\max}$  GH was significantly attenuated after DVP treatment (pre- vs. post-treatment,  $4.34 \pm 3.30$  vs.  $2.78 \pm 3.15$  ng/ml,  $Z = -1.96$ ,  $p = .05$ ). There was also a significant reduction in the AUC GH after DVP treatment compared with pretreatment (pre- vs. posttreatment,  $320.3 \pm 219.8$  vs.  $129.7 \pm 207.2$  ng  $\times$  min/ml;  $Z = -2.52$ ,  $p < .02$ ).

$\Delta$  GH levels at various time points for the eight subjects are plotted in Figure 1. Repeated measures ANOVA on the  $\Delta$  GH data showed a significant time effect ( $F = 3.722$ ,  $df = 6,42$ ,  $p < .006$ ), a significant treatment effect ( $F = 21.667$ ,  $df = 1,7$ ,  $p < .002$ ), but no significant interaction between time and treatment ( $F = 1.38$ ,  $df = 6,42$ ,  $p = .24$ ). Post hoc analyses using Wilcoxon signed-rank test showed a significantly attenuated GH response at 90 min after DVP treatment compared with pretreatment (pre- vs. posttreatment,  $3.84 \pm 3.59$  vs.  $1.09 \pm 1.61$  ng/ml,  $Z = -2.36$ ,  $p < .02$ ).

As shown in Figure 2, there was a significant positive correlation between the changes in  $\Delta_{\max}$  GH response (that is, the pretreatment  $\Delta_{\max}$  GH minus posttreatment  $\Delta_{\max}$  GH) and the blood levels of valproic acid (Spearman's  $r = 0.786$ ,  $p < .03$ ), suggesting that the higher the

**Table 1.** Growth Hormone Responses to Baclofen in Healthy Males before and after Treatment with Divalproex

Subject	Pre-Divalproex				Post-Divalproex			
	Baseline GH	Peak GH	$\Delta_{\max}$ GH	AUC GH	Baseline GH	Peak GH	$\Delta_{\max}$ GH	AUC GH
1	0.94	3.44	2.50	211.1	0.67	1.44	0.77	46.9
2	0.08	2.11	2.03	185.3	0.98	1.42	0.44	-4.9
3	0.67	9.76	9.09	739.5	0.37	9.44	9.07	622.8
4	0.82	2.51	1.69	160.3	1.17	1.60	0.43	-22.8
5	0.33	4.61	4.28	317.4	0.90	6.40	5.50	133.3
6	0.17	1.03	0.86	57.7	0.40	0.80	0.40	39
7	0.80	5.70	4.90	388.6	2.60	6.40	3.80	97.9
8	0.70	10.10	9.40	502.8	0.80	2.70	1.90	125.8
Mean $\pm$ SD	$0.56 \pm 0.32$ —a	$4.90 \pm 3.42$	$4.34 \pm 3.30$ —b	$320.3 \pm 219.8$ —c	$0.98 \pm 0.70$ —d	$3.77 \pm 3.19$	$2.78 \pm 3.15$ —e	$129.7 \pm 207.2$ —f
9	1.39	1.34	-0.05	-83.55	1.04	3.90	2.86	136.6
10	1.05	4.55	3.50	164.2	6.72	5.69	-1.03	-504.3

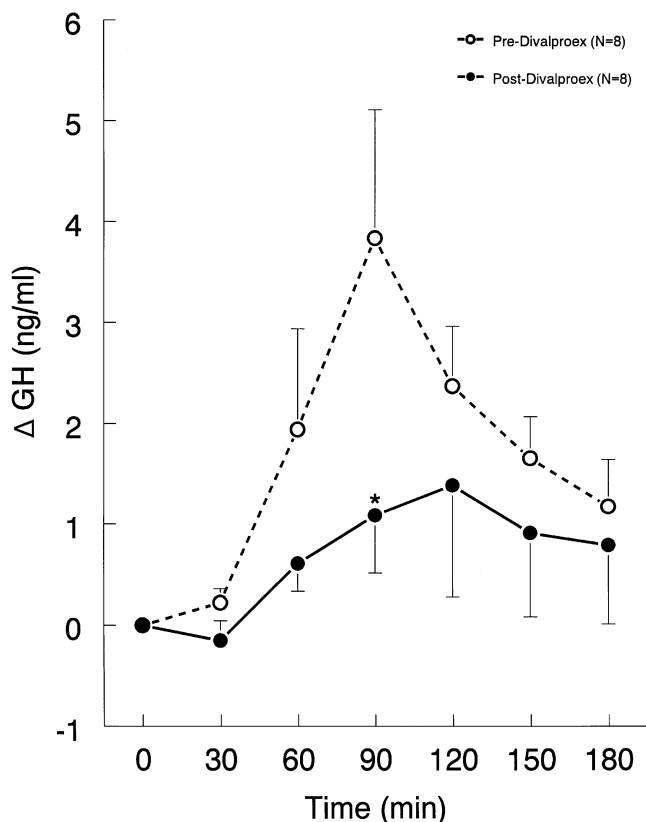
GH = growth hormone (ng/ml);  $\Delta_{\max}$  GH (ng/ml) = peak minus baseline GH levels;

AUC GH (ng  $\times$  min/ml) = growth hormone response to baclofen calculated as net area under curve (AUC<sub>0-180</sub>).

a vs. d:  $p = .12$ , b vs. e:  $p = .05$ , c vs. f:  $p < .02$  (Wilcoxon signed-rank tests).

Subject 9 had the highest baseline GH pretreatment (1.39 ng/ml) and did not have an increase GH response (defined by  $\Delta_{\max}$  GH  $> 0.5$  ng/ml).

Subject 10 had a baseline GH level above 5 ng/ml posttreatment (6.72 ng/ml).



**Figure 1.** Mean ( $\pm$ SEM) GH responses to baclofen in eight healthy males before and after 1 week of DVP treatment. The baclofen-induced GH release was significantly attenuated after DVP treatment compared with those responses pretreatment (repeated measures of ANOVA on  $\Delta$  GH data; Post hoc Wilcoxon signed-rank tests,  $*p < .05$ ).

blood levels of valproic acid, the more attenuated the GH responses to baclofen. There was, however, no significant correlation between the changes in  $\Delta_{\max}$  GH response and age (Spearman's  $r = 0.268$ ,  $p = .52$ ) or body weight (Spearman's  $r = 0.286$ ,  $p = .69$ ).

With regard to behavioral responses, baclofen administration significantly decreased concentration ( $Z = -1.96$ ,  $p = .05$ ) but overall did not have a significant effect on nausea ( $Z = .00$ ,  $p = 1.0$ ), headache ( $Z = -0.38$ ,  $p = .70$ ) or drowsiness ( $Z = -0.48$ ,  $p = .62$ ). DVP treatment did not significantly alter any of these behavioral responses. There were no correlations between  $\Delta_{\max}$  GH levels and  $\Delta$  VAS scores of concentration, nausea, headache, or drowsiness either before or after DVP treatment (data not shown). The adverse events with DVP, which were reported with open questionnaires, included stomach upset and diarrhea (12.5% with mild degree), headache (25% with mild degree), feeling tired (25% with moderate degree), feeling sleepy (12.5% with moderate degree), and feeling moody (12.5% with moderate degree). Three out of the eight subjects did not report any significant side effects.

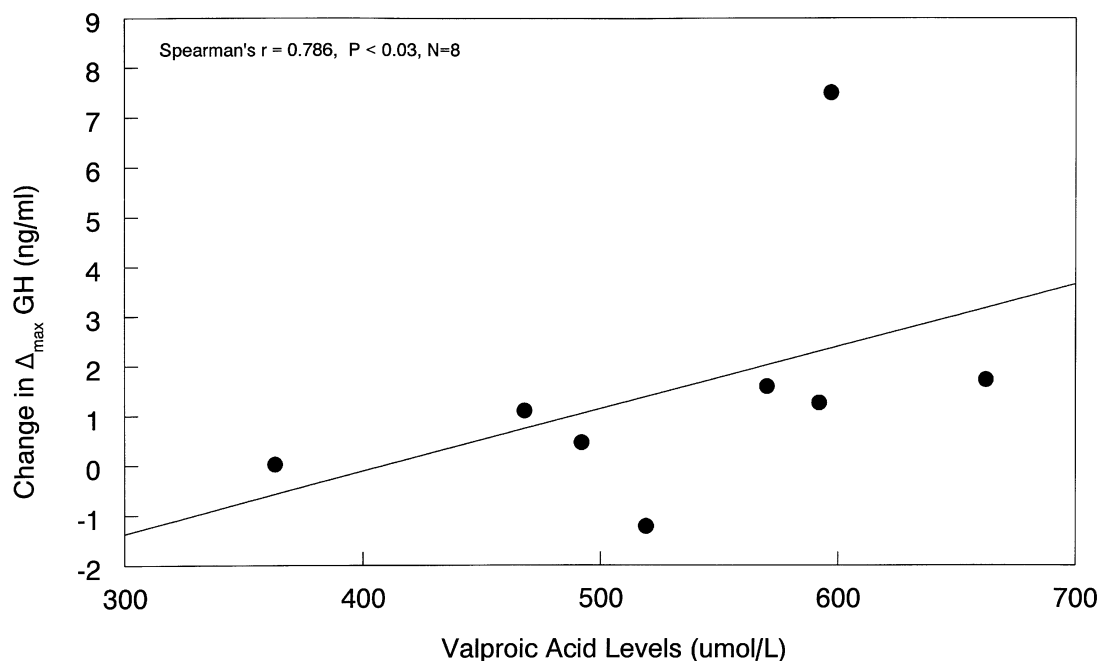
## DISCUSSION

Our major findings in the present study included: (1) administration of baclofen, a GABA<sub>B</sub> receptor agonist, significantly increased plasma GH levels in healthy male humans; (2) 1-week treatment with DVP significantly attenuated the GH response to baclofen; and (3) there was a significant positive correlation between the degree of attenuation of GH responses and the blood levels of valproic acid.

Our finding of an increase in GH release in healthy males after administration of 20 mg of baclofen is consistent with previous studies (Monteleone et al. 1990a, 1990b; O'Flynn and Dinan 1993; Lucey et al. 1994; Davis et al. 1996b) and further supports a role for GABA<sub>B</sub> receptors in modulating GH release in humans. One of our study subjects, however, failed to significantly increase GH response to baclofen. This was also reported in two previous studies, which showed some healthy subjects did not have an increased GH response to 20 mg dose of baclofen (Lucey et al. 1994; Davis et al. 1996b). It is unclear why some normal subjects have little or no GH response to baclofen (Davis et al. 1996b). But, it is of interest to note that in our 10 study subjects, the only subject who did not have an increase in GH response, had the highest baseline GH pretreatment (1.39 ng/ml). Such a finding supports the view that subjects with high baseline GH levels may show blunted response to a subsequent pharmacological challenge (Laakmann et al. 1990; Davis et al. 1996b).

Our finding of an attenuation of GABA<sub>B</sub>-mediated endocrine response to DVP in healthy males suggests that DVP downregulated hypothalamus GABA<sub>B</sub> receptors in the study subjects. Although the sample size for this study was relatively small, the attenuating effect of DVP was further confirmed by the positive correlation between the degree of attenuation measured as change in  $\Delta_{\max}$  GH and the blood levels of valproic acid. Because we did not include a placebo control condition to minimize the effects of confounding variables such as stress effects and variations in baseline hormone levels, we can not exclude the possibility of a Type I error of inference (Thompson et al. 1994). In addition, we did not measure the plasma levels of baclofen. We, therefore, can not exclude the possibility of a pharmacokinetic interaction between baclofen and DVP leading to lower plasma baclofen levels during posttreatment condition, and hence lower GH response. Such, however, seems unlikely as pharmacokinetic data have shown that DVP and baclofen are metabolized through different mechanisms. DVP is metabolized via glucuronidation or oxidation (McNamara 1996), whereas baclofen is excreted unaltered in the urine (85%) or metabolized via deamination (Krogh 1995).

It is of interest to note that our finding is at variance with two rat studies, which demonstrated that chronic



**Figure 2.** The degree of attenuation effect of DVP on baclofen-induced GH response, measured as change in  $\Delta_{\max}$  GH, and the blood levels of valproic acid in eight healthy males. The line indicates a significant positive correlation between change in  $\Delta_{\max}$  GH, and blood levels of valproic acid (Spearman's correlation,  $p < .03$ ).

treatment with sodium valproate significantly increased GABA<sub>B</sub> receptors in the rat hippocampus or frontal cortex (Motohashi 1992; Lloyd et al. 1985). Because these two animal studies did not examine the effect of valproate on the hypothalamic GABA<sub>B</sub> receptors, and that there is, to date, no other study that examined the effect of DVP on GABA<sub>B</sub> receptors in different brain regions, we do not know if valproate treatment alters (up- or downregulates) the hypothalamic GABA<sub>B</sub> receptors in the rat. This raises the possibility that DVP may have differential effects on GABA<sub>B</sub> receptors in different brain regions. That is, DVP may upregulate GABA<sub>B</sub> receptors in the hippocampus or frontal cortex while downregulating those in the hypothalamus. In support of this hypothesis, some indirect evidence has been provided by regional brain studies of rats. Patsalos and Lascelles (1981) showed that that 10 days of treatment with sodium valproate significantly elevated the brain GABA concentrations in several brain regions including the hippocampus, cerebral cortex, pons and medulla, and cerebellum, but produced little change in GABA levels in the hypothalamus, striatum, and mid-brain. Baf et al. (1994) examined the treatment effect of sodium valproate on monoamine levels in different regions of the rat brain. They found that after 45 days of administration of sodium valproate, there was a significant increase in norepinephrine levels in hippocampus and brain stem, whereas a significant decrease was noted in hypothalamus. Serotonin levels were significantly increased in striatum-accumbens, brain stem,

motor cortex, and hippocampus, but they were significantly decreased in hypothalamus and cerebellum. Furthermore, the only animal study that examined the effects of another mood stabilizer, lithium, on GABA receptor binding in hypothalamus, has shown a decrease in [<sup>3</sup>H]-GABA binding sites in rat hypothalamus after chronic administration of lithium (Maggi and Enna 1980). This is in agreement with the result of our study, which showed a downregulation of hypothalamic GABA<sub>B</sub> receptor function with DVP treatment.

An alternative explanation for the discrepancy in findings between our study and the animal studies is species differences in GABA<sub>B</sub> receptor responsivity to valproate between humans and rodents. Consistent with this hypothesis, studies that examined the effects of valproate on 5-HT<sub>1A</sub> receptor responsivity, have demonstrated conflicting results between humans and rats. In humans, we have recently found that DVP significantly attenuates the hypothermic response to ipsapirone, a 5-HT<sub>1A</sub> receptor agonist, in 10 healthy males (Shiah et al. 1997). In rats, however, Khaitan et al. (1994) reported that DVP did not alter the hypothermic response to 8-OH-DPAT (a prototypic 5-HT<sub>1A</sub> receptor agonist). In addition, Monteleone et al. (1990b) reported that 28 days of amitriptyline (100 mg/day) treatment did not significantly alter the GH response to baclofen in eight male depressed patients. A subsequent study by the same group (Monteleone et al. 1990a) reported that 15 and 35 days of treatment with amitriptyline (100 mg/day), imipramine (100 mg/day) and fluoxetine (20

mg/day) also did not modify this endocrine response in 10 male depressed patients, even when a clear therapeutic effect was obtained. These findings are in contrast with those of rat studies that showed an upregulation of GABA<sub>B</sub> receptors after chronic administration of antidepressants (Lloyd et al. 1985; Lloyd and Pichat 1987).

Chronic treatment with DVP (Petty et al. 1996) and ECS (Devanand et al. 1995), but not desipramine (Petty et al. 1993), has been reported to reduce plasma GABA levels in patients with mood disorders. Furthermore, in manic patients treated with DVP (Petty et al. 1996) and in depressed patients receiving ECS (Devanand et al. 1995), higher plasma GABA levels predicted better treatment response. To interpret these data, Petty (1995) formulated a GABA hypothesis for mood disorders. He postulated that low GABA function may be a genetic trait marker of vulnerability for development of mood disorders. Environmental factors, including stress and excessive alcohol use, may increase GABA, causing symptoms of depression or mania. Somatic treatments such as DVP and ECS return GABA to its presymptomatic baseline as the symptoms remit. Given that low GABA<sub>B</sub> receptor function may be associated with depression (Marchesi et al. 1991; O'Flynn and Dinan 1993), our finding of attenuation of GABA<sub>B</sub>-mediated GH response to DVP appears to support Petty's hypothesis. Further studies of the treatment effect of mood stabilizers and ECS on the GH response to baclofen in patients with depression and mania are needed to strengthen this hypothesis.

In summary, we found that DVP treatment significantly attenuated baclofen-induced GH response in humans, and this attenuating effect was related to blood levels of valproic acid. Our findings may suggest that downregulation of GABA<sub>B</sub> receptor function in the hypothalamus is involved in the mechanism of action of DVP in humans. The results of this study should, however, be viewed as preliminary, in light of the small sample size and the lack of placebo control. Further studies are required to replicate our findings before any firm conclusion can be drawn.

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