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# Effects of Divalproex Sodium on 5-$HT_{1A}$ Receptor Function in Healthy Human Males: Hypothermic, Hormonal, and Behavioral Responses to Ipsapirone

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*Hypothermic and hormonal responses to a challenge with a selective 5-$HT_{1A}$ receptor agonist ipsapirone are considered to provide an index of 5-$HT_{1A}$ receptor function in humans. To examine the effects of divalproex sodium (DVP) on 5-$HT_{1A}$ receptor function in humans, we measured the hypothermic, adrenocorticotropic hormone (ACTH) cortisol, and behavioral responses to ipsapirone in 10 healthy male volunteers. After obtaining a blood sample for baseline hormone levels and measuring body temperature, a single dose of 0.3 mg/kg of ipsapirone was given orally to all the subjects and further bloods and temperature reading were obtained at regular intervals for three hours. The ipsapirone challenge tests were repeated after the subjects had been treated with DVP (1000 mg/day) for one week. The results showed that the hypothermia induced by ipsapirone was significantly attenuated by the DVP treatment, whereas the ACTH/cortisol release and the behavioral responses following ipsapirone challenges were not altered. Our findings suggest that DVP may enhance 5-HT neurotransmission in humans via a subsensitization of 5-$HT_{1A}$ autoreceptors but does not appear to affect postsynaptic 5-$HT_{1A}$ receptors.*

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KEY WORDS: *Divalproex sodium; Serotonin; 5-$HT_{1A}$ receptors; Ipsapirone; Hypothermia; ACTH; Cortisol*

Valproate has been shown to be effective in the treatment and prevention of acute mania and somewhat beneficial in the treatment and prevention of depression (Mcelroy et al. 1992). However, the mechanisms of action underlying its efficacy in mood disorders are still unknown. Since disturbances in 5-hydroxytryptamine (5-HT) neurotransmission are implicated in the pathophysiology of mood disorders, it is possible that the efficacy of valproate may be related to its putative actions on 5-HT function.

Several reports have shown that treatment with valproate may enhance central 5-HT function in animals and humans. In rodents for example, valproate increases the synthesis of 5-HT and elevates brain concentration of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Kempf et al. 1982; Shukla 1985; Whitton et al. 1985). More recently, experiments with *in vivo* microdialysis have shown that valproate increased extracellular concentrations of 5-HT in several rat brain regions (Whitton and Fowler 1991; Biggs et al. 1992). In humans, treatment with valproate increased cerebrospinal fluid (CSF) con-

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centrations of 5-HIAA in a patient with post-anoxic intentional myoclonus (Fahn 1978). Maes and colleagues (1994) examined cortisol responses to L-5-hydroxytryptophan (L-5-HTP), a 5-HT precursor, in 10 manic patients before and after 4-6 weeks of treatment with valproate. They found that the L-5-HTP-induced cortisol responses in manic patients were significantly higher after treatment with valproate than before treatment. Since the cortisol responses to L-5-HTP are probably mediated by central 5-HT mechanisms (Maes and Meltzer 1995), their finding suggests that chronic treatment with valproate may enhance central 5-HT function in manic patients.

Ipsapirone hydrochloride, a pyrimidinylpiperzaine 5-$HT_{1A}$ partial agonist (Peroutka 1988), has high affinity and selectivity for 5-$HT_{1A}$ recognition sites and negligible affinity for the 5-$HT_{1B}$, 5-$HT_{1C}$, 5-$HT_{1D}$, 5-$HT_2$, and 5-$HT_3$ subtypes (Lesch 1992). When given orally to humans, it causes dose-dependent increase in adrenocorticotropic hormone (ACTH) and cortisol secretion and decrease in body temperature (Lesch et al. 1989a, 1989b). Pretreatment with pindolol, a β-adrenergic receptor blocker with 5-$HT_{1A}$ receptor antagonistic properties, blocks ACTH and cortisol release as well as hypothermic response, whereas betaxolol, another $\beta_1$-adrenergic blocker without any affinity for 5-$HT_{1A}$ receptors, does not have any effect on hormone release or temperature (Lesch et al. 1990a, 1990b). This would suggest that ACTH and cortisol release, and hypothermia induced by ipsapirone, are indeed mediated by 5-$HT_{1A}$ receptors and that these responses would provide a valid index of 5-$HT_{1A}$ receptor sensitivity in humans (Yatham and Steiner 1993).

In the present study, we examined the effects of valproate on 5-$HT_{1A}$ receptor function in humans by measuring hypothermic, ACTH/cortisol, and behavioral responses to ipsapirone in healthy male volunteers before and after one week treatment with divalproex sodium (DVP).

## METHODS

### Subjects

Ten healthy male volunteers were recruited to participate in the study (mean age ± SD: 29.4 ± 10.5 years). All subjects were screened by a research psychiatrist with a structured clinical interview for DSM-III-R diagnosis-non-patient version (SCID-NP) (Spitzer et al. 1992), a medical history, and a physical examination. All subjects were free of physical and psychiatric illness, and were free of family history of an Axis I psychiatric disorder in first-degree relatives. All subjects were medication free for a minimum of two weeks prior to testing, smoked less than 10 cigarettes per day, and ingested no more than five beers per week and three cups of coffee per day. This study was approved by the Clinical Research Ethics Committee of the University of British Columbia. Written informed consent was obtained from all subjects before enrollment in the study.

### Procedures

Subjects arrived at the Mood Disorders Clinical Research Unit of Vancouver Hospital & Health Science Center between 11:00 A.M. and 11:30 A.M.. They wore normal indoor attire, and after being weighed (mean weight ± SD: 71.6 ± 7.3 kgs), reclined on a bed in a comfortable position with the head elevated. An indwelling intravenous catheter was inserted in a forearm vein at 11:30 A.M. and kept patent by a normal saline infusion. Room temperature ranged between 20° and 22°C. After having had a standard light lunch between 12:00 noon and 12:30 P.M., all subjects were not allowed to eat, sleep or watch television until the procedure was completed, though visits to the bathroom were allowed.

Each subject received 0.3 mg/kg of ipsapirone hydrochloride tablets orally at 2:00 P.M. (time "0"). The average dose ± SD was 22.2 ± 2.6 mg. Sublingual body temperature was recorded at −30, 0, 30, 60, 90, 120, 150, and 180 minutes using a high resolution thermistor probe (IVAC co., San Diego, California), and digital readings were obtained at the end of a 1-minute recording period. For measurement of plasma hormone levels, blood samples were obtained at −30, 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes, collected into prechilled tubes containing EDTA and placed on ice. After collection the samples were immediately centrifuged using a refrigerated centrifuge, and the serum was separated and kept frozen at −80°C for assay at a later time. Behavioral responses to ipsapirone were rated with visual 100 mm analog scales (VAS, 0 = not at all, 100 = most ever) on seven subjective states (nausea, drowsiness, anxiety, headache, depression, concentration, and energy) by the subjects at 0, 60, 120, and 180 minutes. Pulse rates and blood pressure were clinically monitored throughout.

After the pretreatment study, the subjects took 1000 mg/day of DVP (500 mg in the morning and 500 mg in the evening) for one week on an outpatient basis. During the week, they were requested to record any adverse events, which were related to the administration of DVP. The adverse events were classified as mild (not affecting usual activity), moderate (mild disruption in usual activity), and severe (major disruption in usual activity). Subjects took the last dose of DVP at 9:00 A.M. on the 8th day, and ipsapirone challenge was repeated on the same day commencing at 11:00 A.M.. An additional blood sample was taken at the end of ipsapirone challenge test for measuring valproic acid levels to check for compliance (mean valproic acid level ± SD: 629.0 ± 130.7 μmol/L). Dose and drug administration

as well as thermoregulatory, endocrine, and behavioral monitoring were identical to the pretreatment studies.

### Biochemical Assays

The assays were performed in the Clinical Chemistry Laboratory, Vancouver General Hospital. Valproic acid plasma concentrations were determined using fluorescence polarization immunoassay (FPIA) technology. ACTH and cortisol were measured by radioimmunoassay (Ciba Corning Diagnostic Corp, USA). Inter- and intra-assay coefficients of variation were 7.8% and 3.0% for ACTH and 4.0% and 2.0% for cortisol. All plasma samples from a given subject were assayed in the same batch, and all assays were performed by a lab technician blind to the study conditions.

### Statistics

Both temperature and hormonal data at time "−30" and "0" points before and after DVP treatment did not differ and were averaged to obtain a single baseline value for each variable. Baseline body temperature and hormone differences were assessed by paired *t*-tests. The hypothermic and hormonal responses to ipsapirone were calculated as : 1) the net change from baseline at each timepoint (labeled as Δ); and 2) the net maximal response (labeled as $\Delta_{max}$), that is, the peak response minus baseline. Repeated measures analyses of variance (ANOVA) and covariance (ANCOVA) were used to examine the treatment effect of DVP on the hypothermic and hormonal responses measured by the net change from the baseline. Post-hoc tests were carried out using paired *t*-tests. The $\Delta_{max}$ data were not normally distributed and were analyzed with Wilcoxon's sign rank tests. Changes in visual analogue ratings (peak response minus baseline) were also assessed by Wilcoxon's sign rank tests. Relationships between variables were assessed by means of Pearson's product moment correlation. Because of the large number of correlations performed, the significance level was set at $P < .01$. All significant levels reported were two-tailed. Data were reported as mean, plus or minus standard deviation. The data were analyzed by using statistical package for social sciences (SPSS) software.

## RESULTS

### Hypothermic Responses

There was a trend toward lower baseline body temperature (36.7 ± 0.4 vs. 36.6 ± 0.2°C; $t = 2.17$, $df = 9$, $P = .06$) after DVP treatment compared with pretreatment. Before the DVP treatment ipsapirone (0.3 mg/kg) produced a significant hypothermic response. However, following one week of DVP, the hypothermic response was significantly attenuated (Figure 1). Repeated measures ANCOVA using pre- and post-treatment baseline body temperature as covariates showed a trend for treatment effect ($F = 4.56$, $df = 9,1$, $P = .06$), a significant time effect ($F = 10.11$, $df = 54,6$, $P < .001$) and a significant interaction effect ($F = 3.96$, $df = 54,6$, $P < .003$). Post hoc analyses using paired *t* tests showed a significantly attenuated hypothermia at 120, 150, 180 minutes after DVP treatment compared to pre-treatment ($t = -2.35$, $df = 9$, $P < .05$; $t = -4.33$, $df = 9$, $P < .003$; $t = -2.28$, $df = 9$, $P < .05$, respectively). As shown in Figure 2A, the ipsapirone-induced hypothermic response as measured by $\Delta_{max}$ body temperature was also significantly attenuated after the DVP treatment when compared with pre-treatment (pre- vs. posttreatment, −0.63 ± 0.3 vs. −0.40 ± 0.2°C; $Z = -2.07$, $P < .05$).

### Plasma ACTH Responses

There was no significant difference in baseline plasma ACTH levels in ten subjects before and after DVP treatment (3.6 ± 1.6 vs. 2.8 ± 2.7 pmol/L; $t = -0.91$, $df = 9$, $P = .38$). Repeated measures ANOVA on Δ ACTH data showed a trend for time effect ($F = 2.50$, $df = 4,36$, $P = .06$), but no treatment effect ($F = 0.04$, $df = 1,9$, $P = .85$) or interaction between time and treatment ($F = 1.20$, $df = 4,36$, $P = .33$) (Figure 3). Furthermore, the plasma ACTH response to ipsapirone measured by $\Delta_{max}$ was also not altered by the DVP treatment (11.1 ± 17.5 vs. 10.7 ± 20.3 pmol/L; $Z = -0.26$, $P = .80$) (Figure 2B).

### Plasma Cortisol Responses

There was no significant difference in baseline plasma cortisol levels in ten subjects between pre- and post-treatment conditions (216.7 ± 63.5 vs. 305.1 ± 158.9 nmol/L; $t = -2.02$, $df = 9$, $P = .08$). Repeated measures ANOVA on Δ cortisol data showed a significant time effect ($F = 5.32$, $df = 10,90$, $P < .001$) but no treatment effect (F = 0.16, $df = 1,9$, $P = .70$) or an effect for treatment × time interaction ($F = 1.72$, $df = 10,90$, $P = .09$) (Figure 4). In addition, the plasma cortisol response to ipsapirone measured by $\Delta_{max}$ was not altered by the DVP treatment, either (227.0 ± 133.1 vs. 202.1 ± 216.7 nmol/L; $Z = -0.05$, $P = .96$) (Figure 2C).

### Behavioral Responses and Adverse Events

We compared the maximal behavioral responses independent of time with baseline responses using Wilcoxon's sign rank tests. We found that ipsapirone overall significantly increased drowsiness ($Z = -2.82$, $P < .005$), nausea ($Z = -2.50$, $P < .02$), headache ($Z = -2.22$, $P < .03$) and anxiety ($Z = -2.13$, $P < .04$), decreased energy ($Z = -3.36$, $P < .001$), and concentration ($Z = -2.90$, $P < .004$), but had no significant effect on

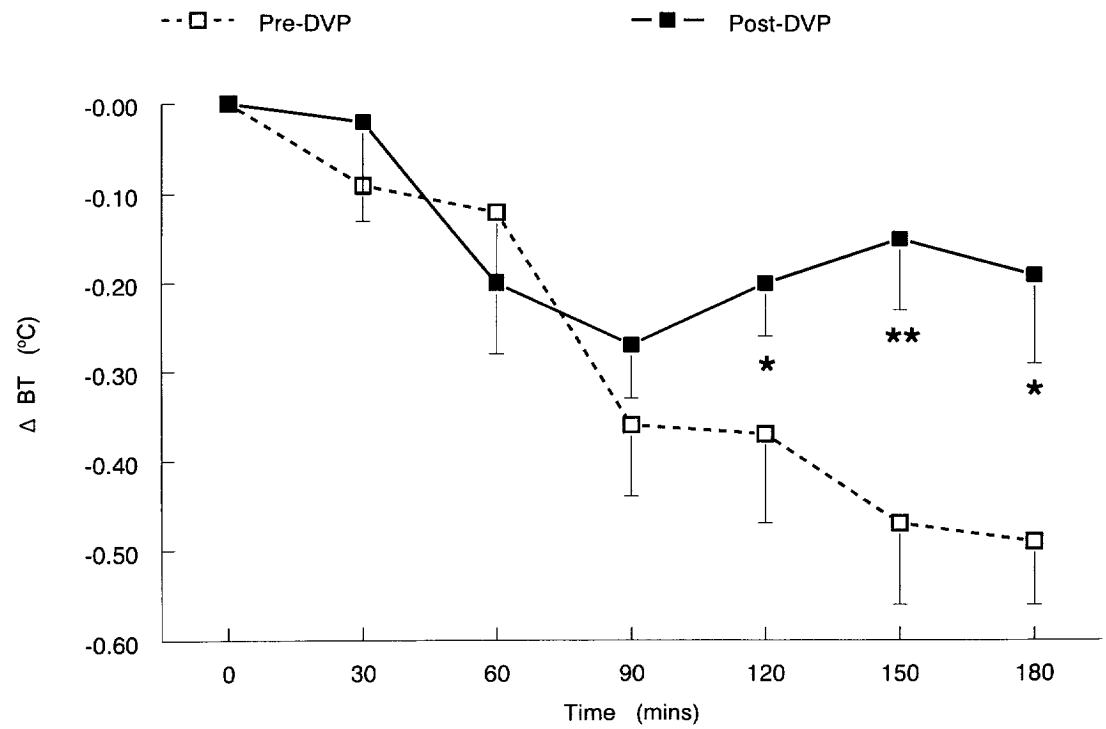


**Figure 1.** Mean (± SEM) hypothermic response (measured as change from baseline, Δ BT) following ipsapirone administration in ten healthy human males before and after Divalproex (DVP) treatment. The hypothermic responses to ipsapirone were significantly attenuated after DVP treatment compared with those responses pretreatment (Repeated measures of ANOVA) (Post hoc paired *t* tests, $^*P < .05$, $^{**}P < .005$).

depression ($Z = -1.34$, $P = .18$). However, none of the behavioral responses measured as $\Delta_{max}$ VAS scores was significantly altered by DVP treatment (data not shown). The adverse events with DVP, which were reported with open questionnaires, included headache (10% with mild, moderate, and severe degree respectively), drowsiness (20% with mild degree and 10% with moderate degree), nausea (20% with moderate degree), diarrhea (10% with mild degree), and feeling tired (10% with mild degree). In addition, one subject

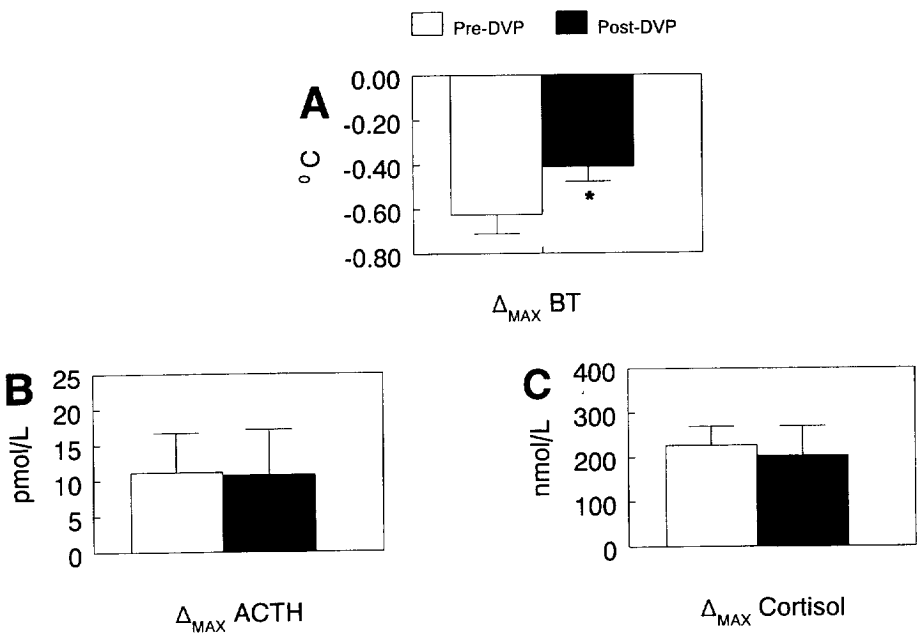


**Figure 2.** Mean (± SEM) net maximal hypothermic and hormonal responses (labeled as $\Delta_{max}$ BT, $\Delta_{max}$ ACTH, $\Delta_{max}$ Cortisol) to ipsapirone before and after DVP treatment. (**A**) The net maximal hypothermic responses to ipsapirone were significantly attenuated after the DVP treatment compared with those responses pretreatment (Wilcoxon's sign rank tests, $^*P < .05$). (**B**) and (**C**) DVP treatment did not alter the net maximal plasma ACTH/cortisol responses to ipsapirone (Wilcoxon's sign rank tests).

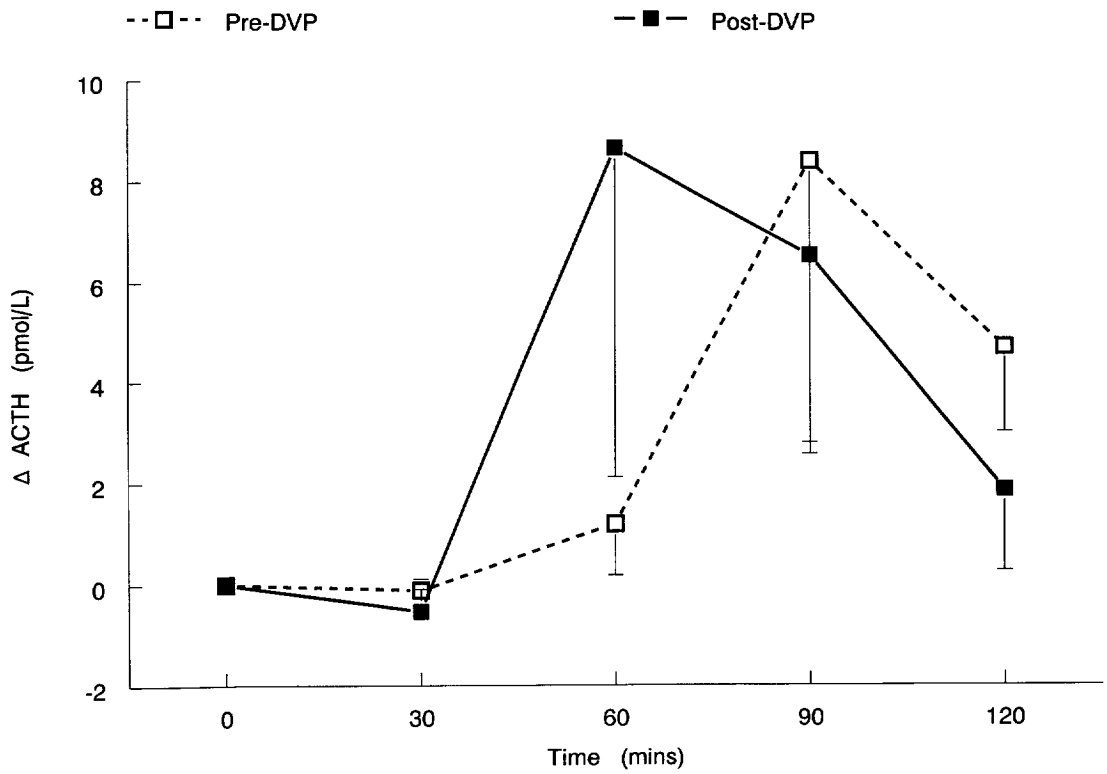


**Figure 3.** Mean (± SEM) plasma ACTH responses (measured as change from baseline, Δ ACTH) following ipsapirone administration in 10 healthy human males before and after DVP treatment. DVP treatment did not significantly alter the ACTH responses to ipsapirone (repeated measures of ANOVA).

reported mild gum bleeding in the first two days of the drug administration but the symptom spontaneously vanished. Another reported vomiting once on the second day of the drug administration. Three out of the ten subjects did not report any significant side effects.

### Relationship Between Variables

There were no significant correlations between $\Delta_{max}$ hypothermic response and ACTH or cortisol responses either before or after DVP treatment. There were no significant correlations between plasma valproic acid levels and $\Delta_{max}$ hypothermic, ACTH or cortisol responses posttreatments. There was a significant correlation between the $\Delta_{max}$ VAS scores of anxiety and the $\Delta_{max}$ hypothermic responses ($r = 0.91$, $P < .001$) before DVP treatment, but there were no significant correlations between any other behavioral responses to ipsapirone and the hypothermic or endocrine responses either before or after DVP treatment.

## DISCUSSION

Our major findings were: 1) ipsapirone significantly decreased body temperature and increased plasma cortisol levels in healthy human males; there was a strong trend toward an increase in plasma ACTH levels to ipsapirone challenge; 2) one week treatment with DVP significantly attenuated the hypothermia induced by ipsapirone, but it had no effect on the ACTH and cortisol responses to ipsapirone; and 3) ipsapirone significantly decreased energy, and concentration, and increased anxiety, headache, drowsiness, and nausea, but there were no significant treatment effects of DVP on these behavioral responses.

### 5-$HT_{1A}$-Mediated Hypothermic Responses

Our study demonstrated a significant hypothermic effect of ipsapirone in healthy men. This is consistent with previous findings that 5-$HT_{1A}$ receptor agonists such as buspirone (Anderson and Cowen 1992), ipsapirone (Lesch et al. 1990b) gepirone (Anderson et al. 1990), and flesinoxan (Seletti et al. 1995) induced hypothermia in humans. The hypothermic response induced by ipsapirone in humans is antagonized by pindolol pretreatment, suggesting that the response is 5-$HT_{1A}$ receptor mediated (Lesch et al. 1990b).

There has been some controversy in the animal literature about whether hypothermia induced by 5-$HT_{1A}$

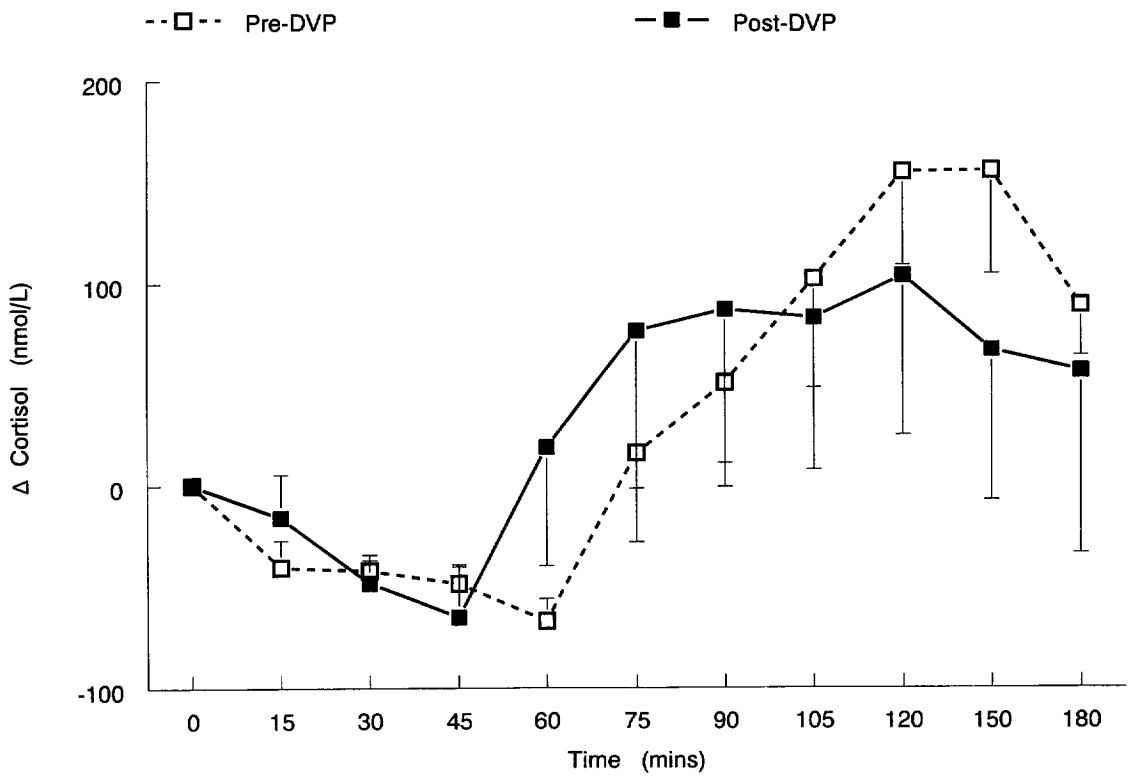


**Figure 4.** Mean (± SEM) plasma cortisol responses (measured as change from baseline, Δ cortisol) following ipsapirone administration in 10 healthy human males before and after DVP treatment. DVP treatment did not significantly alter the cortisol responses to ipsapirone (repeated measures of ANOVA).

agonists is mediated by somatodendritic autoreceptors or postsynaptic 5-HT$_{1A}$ receptors. There is clear evidence that in mice, the hypothermic response to the prototypic 5-HT$_{1A}$ agonist 8-hydroxy-2-(di-n-propylamino)tetraline (8-OH-DPAT) is mediated by presynaptic 5-HT$_{1A}$ receptors because the hypothermia induced by 8-OH-DPAT is abolished by : 1) destruction of presynaptic 5-HT neurons with the neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT) (Goodwin et al. 1985a; Martine et al. 1992); and 2) depletion of 5-HT stores by a pretreatment with parachlorphenylalanine (pCPA), an inhibitor of 5-HT synthesis (Goodwin et al. 1985a). This was replicated by Bill et al. (1991) who also showed that both 5,7-DHT lesions and pCPA treatment led to a significant decrease in brain 5-HT, as well as 5-hydroxyindoleacetic acid (5-HIAA) levels in mice. Furthermore, they also demonstrated that pretreatment with agents which facilitate 5-HT release acutely such as selective serotonin reuptake inhibitors (SSRIs), the 5-HT precursor 5-hydroxytryptophan (5-HTP), or a 5-HT releasing agent fenfluramine, markedly attenuated or abolished the 8-OH-DPAT induced hypothermia in this species. Taken together, these findings would suggest that an autoreceptor mediated inhibition of 5-HT release, on to an (as yet) unidentified postsynaptic 5-HT receptor, is primarily responsible for the hypothermic response in mice (Bill et al. 1991).

However, the findings for rats are much less consistent. Goodwin et al (1987) reported that pCPA administration for two weeks led to attenuation of 8-OH-DPAT-induced hypothermia. Hillegaart (1991) found that a direct injection of 8-OH-DPAT into 5-HT cell bodies in the dorsal raphe nucleus of rats led to clear hypothermia. These results suggest that the 5-HT$_{1A}$ receptors mediating hypothermia in rats are located presynaptically. In contrast, Hjorth (1985) and Hutson et al. (1987) reported that 5,7-DHT lesions or pCPA treatment enhanced 8-OH-DPAT-induced hypothermia, suggesting that the relevant 5-HT$_{1A}$ receptors are located postsynaptically. Further evidence in support of the hypothesis that hypothermia in rats is mediated by postsynaptic 5-HT$_{1A}$ receptors has been provided by O'Connell et al. (1992) who showed that pretreatment with pCPA did not affect the 8-OH-DPAT- or BMY 7378-(BMY 7378 is a buspirone analogue with 5-HT$_{1A}$ receptor agonist properties) induced hypothermia in rats (O'Connell et al. 1992). In addition, Bill et al. (1991) found no effect of 5-HTP or fenfluramine on 8-OH-DPAT-induced hypothermia in rats; since these drugs increase 5-HT secretion, they would be expected to antagonize hypother-

mia induced via activation of 5-$HT_{1A}$ presynaptic receptors. Taken together, the findings of the studies performed in rats suggest that the 8-OH-DPAT-induced hypothermia in rats is probably mediated by a mixed pre- and postsynaptic 5-$HT_{1A}$ receptor activation.

Given the discrepancy in the mechanism of 8-OH-DPAT-induced hypothermia between mouse and rat, it is hard to generalize the findings of rodent studies to humans. To our knowledge, there is only one human study to date that addressed this issue. Blier et al. (1994), using the hypothermic response to buspirone as an index of 5-$HT_{1A}$ receptor function in healthy volunteers, reported that tryptophan depletion paradigm had no effect on the buspirone induced hypothermia. Based on this, they concluded that hypothermia induced by 5-$HT_{1A}$ receptor agonists in humans was mediated by an activation of postsynaptic 5-$HT_{1A}$ receptors (Blier et al. 1994). However, in humans buspirone does not appear to induce hypothermia consistently (Lee and Meltzer 1991), suggesting that buspirone-induced hypothermia is not likely to be a good measure of 5-$HT_{1A}$ receptor function. Furthermore, if the hypothermic responses to 5-$HT_{1A}$ agonists in humans, like 5-$HT_{1A}$-mediated ACTH/cortisol responses, are mediated by an activation of postsynaptic 5-$HT_{1A}$ receptors, an unaltered hypothermic response to ipsapirone would be expected after DVP treatment given that in the present study the endocrine responses were not affected by DVP. However, we found that DVP treatment attenuated the hypothermic response to ipsapirone but did not affect endocrine responses. Therefore, our results are consistent with the hypothesis that hypothermic response to ipsapirone in humans is mediated by presynaptic receptors, and that DVP alters 5-HT neurotransmission by affecting presynaptic 5-$HT_{1A}$ autoreceptors but not postsynaptic 5-$HT_{1A}$ receptors.

Previous studies have demonstrated that chronic treatment with amitriptyline in depressed patients (Lesch et al. 1990c), fluoxetine in patients with obsessive compulsive disorder (OCD) Lesch et al. 1991), paroxetine in healthy subjects (Wing et al. 1996), and various antidepressant treatments including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), SSRIs, electroconvulsive shock (ECS) and lithium in mice (Goodwin et al. 1985b, 1986, Maj and Moryl 1992; Martin et al. 1992), attenuated hypothermic responses to 5-$HT_{1A}$ receptor agonists. Our finding of an attenuation of ipsapirone-induced hypothermia by DVP in healthy males is consistent with these earlier reports, suggesting that subsensitivity of the 5-$HT_{1A}$ autoreceptors may be a change induced by most antidepressant treatments and could serve as an important factor in their therapeutic action. However, it is of some interest to note that a recent study in rats did not find any effect of valproate on hypothermia induced by 8-OH-DPAT (Khaitan et al. 1994). The discrepancy in findings between our study and the rat study is likely to be due to species differences in the responsivity of 5-$HT_{1A}$ receptors to valproate treatment.

### 5-$HT_{1A}$-Mediated Hormonal Responses

Given in sufficient doses, ipsapirone and other 5-$HT_{1A}$ receptor agonists increase plasma ACTH and cortisol in rodents and humans (Urban et al. 1986; Koenig et al. 1987; Gilbert et al. 1988; Cowen et al. 1990). The endocrine responses elicited by the 5-$HT_{1A}$ receptor agonists have been shown to be mediated by postsynaptic 5-$HT_{1A}$ receptors which stimulate corticotropin-releasing hormone (CRH) release in the paraventricular nucleus (PVN) of the hypothalamus (Koenig et al. 1987; Gilbert et al. 1988; Bagdy and Makara 1994). Our results showed that ipsapirone significantly increased plasma cortisol/ACTH levels in humans, supporting a role for 5-$HT_{1A}$ receptor in regulating hypothalamic-pituitary-adrenal (HPA) axis activation.

In regards to the effects of psychotropic drugs on the postsynaptic 5-$HT_{1A}$ receptor-mediated endocrine responses, Aulakh et al. (1988) reported that repeated treatment of rats with imipramine, clomipramine, or clorgyline had no effect on the rise of ACTH caused by 8-OH-DPAT. Gartside et al. (1992) reported that the ACTH response to 8-OH-DPAT in rats was unaffected by amitriptyline, electroconvulsive shock (ECS), or lithium. Li and colleagues (1993, 1994) demonstrated that chronic treatment with fluoxetine, but not desipramine, attenuated the endocrine responses to 8-OH-DPAT and ipsapirone in male rats. More recently, Akiyoshi et al. (1995) investigated 8-OH-DPAT-induced cortisol in male rats after treatment with mianserin (2, 10 mg/kg), imipramine (5 mg/kg), desipramine (5 mg/kg), and doxepine (5 mg/kg) for 1 day or 3 weeks. They found that chronic mianserin (10 mg/kg) and doxepine significantly increased the 8-OH-DPAT-induced cortisol response, whereas acute antidepressants and chronic imipramine, desipramine, mianserin (2 mg/kg) treatment did not change it.

In human studies, Lesch et al. (1991) reported that a significant reduction in postsynaptic 5-$HT_{1A}$-mediated ACTH/cortisol responses was obtained during a course of fluoxetine treatment in patients with OCD, and Wing and colleagues (1996) found that 16 days treatment with paroxetine (30 mg/day) produced an attenuation of endocrine responses to gepirone in healthy humans. In contrast, Walsh et al. (1991) reported that ACTH/cortisol responses induced by gepirone in healthy males were not altered by seven days of lithium treatment (800 mg/day), and Lesch (1991) reported that the ACTH and cortisol responses to ipsapirone were not altered during chronic treatment with amitriptyline in depressed patients. In a recent study we have found that treatment with lamotrigine, a newer anticonvul-

sant with antimanic and antidepressant properties, had no effect on the cortisol response to ipsapirone in healthy humans (Shiah et al. 1997). In addition in the present study, one week treatment with DVP (1000 mg/day) did not alter the ACTH/cortisol responses to ipsapirone in healthy males. This may suggest that DVP does not affect postsynaptic 5-$HT_{1A}$ receptors. Taken together, the results of the present study and the previous animal and human endocrine studies suggest that the ACTH/cortisol responses to 5-$HT_{1A}$ receptor agonists appear to be attenuated by SSRIs such as fluoxetine and paroxetine, but not by other antidepressant treatments including TCAs, MAO-Is, electroconvulsive therapy, and mood stabilizers such as lithium, DVP, and lamotrigine. However, the mechanism by which SSRIs attenuate 5-$HT_{1A}$ receptor-mediated hormone responses is still unclear.

In conclusion, we found that DVP attenuated the hypothermia induced by ipsapirone but did not alter the hormonal and behavioral responses, suggesting that DVP may enhance 5-HT neurotransmission via a subsensitization of 5-$HT_{1A}$ autoreceptors, but does not appear to have an effect on postsynaptic 5-$HT_{1A}$ receptors. Studies of 5-$HT_{1A}$-mediated function after DVP treatment in patients with mood disorders may further establish the role of 5-$HT_{1A}$ receptors in the mechanisms of action of DVP in mood disorders.

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