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Effects of Carbamazepine on Pituitary-Adrenal Function in Healthy Volunteers*

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ABSTRACT. Carbamazepine (CBZ) is a widely used therapeutic agent in seizure, pain, and mood disorders. Although CBZ has been shown to inhibit hypothalamic CRH secretion *in vitro*, limited data suggest that systemic CBZ induces pituitary-adrenal activation. Few data are available to reconcile these effects or clarify their mechanism(s), particularly in healthy human subjects.

We report here a study of basal ACTH and cortisol secretion and their responses to ovine CRH administration in nine healthy volunteers, studied both during repeated (2–3 weeks) administration of CBZ and while medication free. CBZ significantly increased mean 24-h urinary free cortisol (mean ± SE, 197 ± 17 *vs.* 137 ± 24 nmol/day; $P < 0.02$) and evening basal total plasma cortisol (113 ± 17 *vs.* 83 ± 14 nmol/L; $P < 0.05$) as well as cortisol-binding globulin-binding capacity (497 ± 36 *vs.* 433 ± 28 nmol/L; $P < 0.01$). Despite the CBZ-induced hypercortisolism, plasma ACTH responses to CRH during CBZ treatment remained robust, rather than being suppressed by basal hypercortisolism. In fact, during CBZ treatment, we noted a positive correlation between the increase in basal plasma cortisol and the increase in the plasma ACTH response to CRH ($r = 0.65$; $P < 0.05$). We also observed a reduction in cortisol-binding globulin-binding capacity after CRH administration (315 ± 25 *vs.* 433 ± 28 nmol/L; $P < 0.001$), which was accentuated by CBZ treatment (342 ± 19 *vs.* 497 ± 36 nmol/L; $P < 0.001$; magnitude of fall, −155 ± 22 nmol/L on CBZ *vs.* −118 ± 11 nmol/L off CBZ; $P < 0.05$).

We conclude that CBZ increases plasma cortisol secretion in healthy volunteers independent of its effect on plasma cortisol-binding capacity. This pituitary-adrenal activation seems to reflect a pituitary, rather than a hypothalamic, effect of CBZ. Hence, despite CBZ-induced hypercortisolism, the ACTH response to CRH remained robust in direct proportion to the CBZ-induced rise in basal plasma cortisol. Thus, we propose that the increased cortisol secretion observed during CBZ treatment reflects a relative inefficacy of glucocorticoid negative feedback at the pituitary. This pituitary-driven increase in cortisol secretion combined with the expected reduction in centrally directed CRH secretion could contribute to the anticonvulsant properties of CBZ. (*J Clin Endocrinol Metab* **74:** 406–412, 1992)

CARBAMAZEPINE (CBZ) is a tricyclic agent with therapeutic efficacy in a broad range of conditions, including complex partial seizures, paroxysmal pain disorders, and major affective disorder (1). Recent reports have indicated that CBZ influences hypothalamic-pituitary-adrenal (HPA) function in both humans (2–4) and experimental animals (5). However, the precise nature of these effects has not been fully characterized, nor have their mechanisms been definitively elucidated. In the light of data suggesting that elements of the HPA axis, such as CRH and cortisol, can influence both neuronal excitability (6–8) and certain aspects of the symptom complex of major affective disorder (9–11), the effects of CBZ on specific components of the HPA axis may be relevant to its therapeutic efficacy in these various disorders.

We report here a longitudinal study in healthy volunteers in which HPA function was evaluated during drug-free and CBZ treatment periods. To explore whether CBZ influences HPA function via peripheral or central mechanisms in humans, we evaluated the functional responsiveness of the pituitary corticotroph in these volunteers by assessing basal plasma immunoreactive ACTH and cortisol levels and their responses to ovine CRH administration. We also measured cortisol-binding globulin (CBG)-binding capacity at baseline and after CRH administration and obtained serial measures of urinary free cortisol (UFC) excretion. Because arginine vasopressin (AVP) can release ACTH in a fashion that is independent of glucocorticoid negative feedback (12)

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while acting synergistically with CRH at the pituitary corticotroph cell (13, 14), we attempted to assess the effects of CBZ on AVP secretion and actions. In this regard, previous data indicate that CBZ produces an antidiuretic effect by enhancing renal responsiveness to AVP (15). We reasoned that if an analogous effect occurred at the pituitary corticotroph cell, it might be reflected in the ACTH responses to CRH and glucocorticoid negative feedback.

Materials and Methods

Subjects and procedures

Subjects consisted of nine volunteers [six females and three males; mean age, 36.1 ± 2.5 yr (±SE] who were evaluated and found by history, physical examination, and laboratory testing to have no evidence of cardiovascular, renal, hepatic, hematological, neurological, or endocrine disease. Subjects showed no evidence of major psychiatric illness by a structured psychiatric interview (SADS-L) (16). Subjects were tested while medication free for at least 4 weeks and again after having taken CBZ for 2–3 weeks at doses producing serum concentrations within the accepted therapeutic range for seizure control (5–10 μL). The dosage of CBZ ranged from 500–800 mL/day, and the mean serum CBZ level was 8.1 ± 0.5 μg/mL (±SEM; range, 5.6–9.9 μL/mL). In eight of these volunteers, three consecutive 24-h urine collections were performed, ending on the morning of CRH testing, for UFC and osmolality determinations. CRH stimulation testing was conducted using 1 μg/kg ovine CRH (Bachem, Torrance, CA), administered at 2000 h by iv bolus through an indwelling catheter placed at least 1 h before starting blood sampling, as previously described (17–19). Plasma immunoreactive (IR-) ACTH and cortisol levels were measured at baseline (every 15 min from −120 to 0 min and at −8 min) and 5, 15, 30, 60, 90, and 120 min after CRH administration. Plasma IR-ovine CRH was measured 30, 60, 90, and 120 min after each dose to assess its disappearance rate. In eight subjects, the CBG-binding capacity was measured 0 and 60 min after CRH administration. In seven subjects, plasma IR-AVP was measured every 15 min from −90 to 0 min and at −8 min. Subjects gave written informed consent for the study, which was conducted under institutional clinical research subpanel-approved protocols.

Hormone assays

Plasma ACTH and AVP were measured by RIA after Sep-Pak C-18 (Waters, Inc., Milford, MA) extraction, and cortisol by RIA of unextracted plasma, as previously described (14, 17) except for the use of a different anti-AVP antiserum (Amell Products Corp., New York, NY). Detection limits were 0.4–0.7 pmol/L for ACTH, 0.3 pmol/L for AVP, and 5.5 nmol/L for cortisol. The intraassay coefficient of variation (cv) was 7.0% for ACTH, 8% for AVP, and 4.2% for cortisol; all samples were assayed concurrently. Plasma ovine CRH was measured by RIA in serial dilutions of plasma, as previously described (17). The detection limit was 6.6 pmol/L. The intraassay cv was 8%; all samples were measured in the same assay. UFC was measured by SmithKline Beecham Laboratories (Philadelphia, PA), using reagents from Diagnostic Products, Inc. (Los Angeles, CA). CBG-binding capacity was measured by competitive binding of [^{3}H]cortisol after Concanavalin-A-Sepharose adsorption, as described previously (20). The intraassay cv was 8.9%; all samples were measured in the same assay. A plasma free cortisol index was calculated from the total plasma cortisol level, CBG-binding capacity, and albumin concentration by a previously described (21) and validated (22) computer model (TRANSPORT). Urinary osmolality was measured in aliquots from 24-h urine collections by freezing point depression (Advanced Instruments, Needham Heights, MA), with calibrated standards included in each run.

Statistical analysis

The total integrated ACTH and cortisol responses were calculated as the area beneath the concentration-time curve from 0–120 min, using the trapezoidal method. The net integrated ACTH and cortisol responses were calculated as the difference between the total integrated response and the mean basal (−15 to 0 min) level × 120 min. Group means of the on and off CBZ basal and stimulated values were compared by paired two-tailed Student's t tests. Pearson correlation coefficients were used throughout.

Results

Basal ACTH and cortisol secretion

The mean 24-hour UFC excretion for the 3 days immediately preceding CRH stimulation testing was significantly increased during CBZ treatment compared to that in the medication-free state (197 ± 17 *vs.* 137 ± 24 nmol/day; $P < 0.02$; Fig. 1A). Moreover, the mean basal plasma cortisol level in these volunteers, averaged over the entire 2-h basal sampling period, was significantly elevated during CBZ treatment compared to that in the medication-free state (113 ± 17 *vs.* 83 ± 14 nmol/L; $P < 0.05$; Fig. 1B). The mean CBG-binding capacity at time zero was also significantly increased during CBZ treatment (497 ± 36 *vs.* 433 ± 28 nmol/L; $P < 0.01$; Fig. 1C); the basal plasma free cortisol index at this time was slightly but not significantly increased (2.9 ± 0.7 on CBZ *vs.* 2.0 ± 0.6 nmol/L off CBZ; $P < 0.15$; Fig. 1D).

Basal plasma ACTH levels were not significantly affected by CBZ (2.31 ± 0.22 on CBZ *vs.* 2.22 ± 0.20 pmol/L off medication; P = NS).

Plasma ACTH and cortisol responses to CRH

The plasma ACTH and cortisol responses to CRH in the volunteers studied on and off CBZ are shown in Fig. 2. There was a trend toward greater net integrated (220.4 ± 51.3 on CBZ *vs.* 184.1 ± 30.2 pmol/L·120 min off CBZ) and peak (5.84 ± 0.88 on CBZ *vs.* 5.11 ± 0.35 pmol/

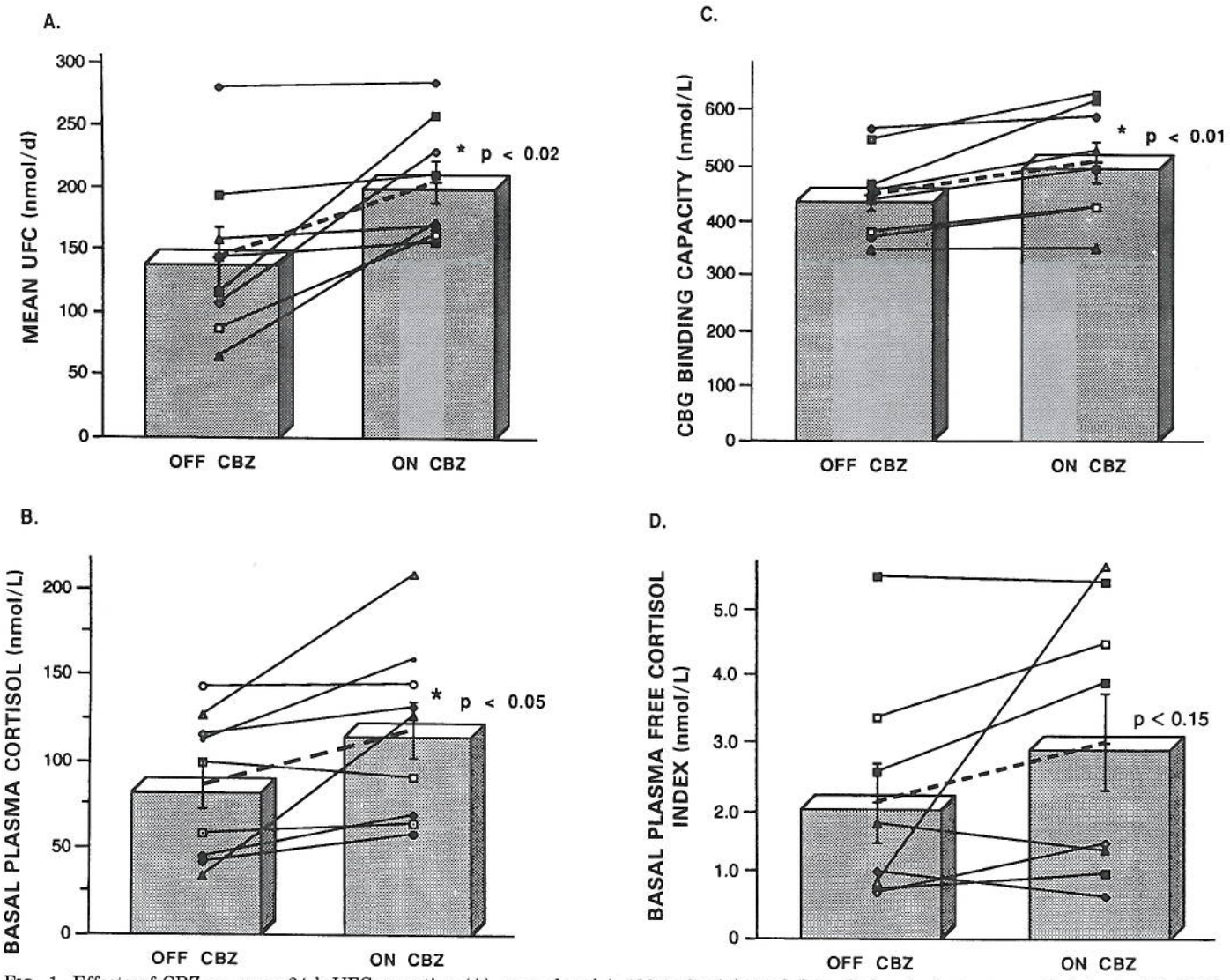

FIG. 1. Effects of CBZ on mean 24-h UFC excretion (A), mean basal (−120 to 0 min) total (bound plus free) plasma cortisol levels (B), CBG-binding capacity at 0 min (C), and basal (0 min) plasma free cortisol index (D) in healthy volunteers (n = 9 for B; n = 8 for all other measures). CBZ was given as described in *Materials and Methods*. *Symbols connected by solid lines* represent data from individual subjects; *bars* represent the mean ± SEM; the *heavy dashed line* shows a trend in mean across subjects between off and on CBZ conditions.

L off CBZ) ACTH responses to CRH during CBZ treatment. The plasma free cortisol response to CRH was slightly but not significantly reduced during CBZ treatment (41.2 ± 5.6 on CBZ *vs.* 61.4 ± 10.5 nmol/L off CBZ; $P < 0.15$; Fig. 3). The net integrated total (bound plus free) plasma cortisol response during the CRH stimulation test was also slightly but not significantly reduced during the drug-free and CBZ treatment periods (28.56 ± 1.66 on CBZ *vs.* 33.11 ± 4.61 μmol/L·120 min off CBZ; $P < 0.15$). The disappearance rate of plasma IR-ovine CRH after CRH administration did not differ on and off CBZ in these subjects (data not shown).

Relationship between the effect of CBZ on ACTH and cortisol responses to CRH and that on basal pituitary adrenal function

There was a significant positive correlation between the CBZ-induced increases in the peak ACTH response to CRH and basal total plasma cortisol ($r = 0.65$; $P < 0.05$; Fig. 4). A similar relationship was observed between the change in the peak ACTH response and the change in basal plasma free cortisol ($r = 0.88$; $P < 0.01$). There was also a significant positive correlation between the peak ACTH response and the basal plasma cortisol level

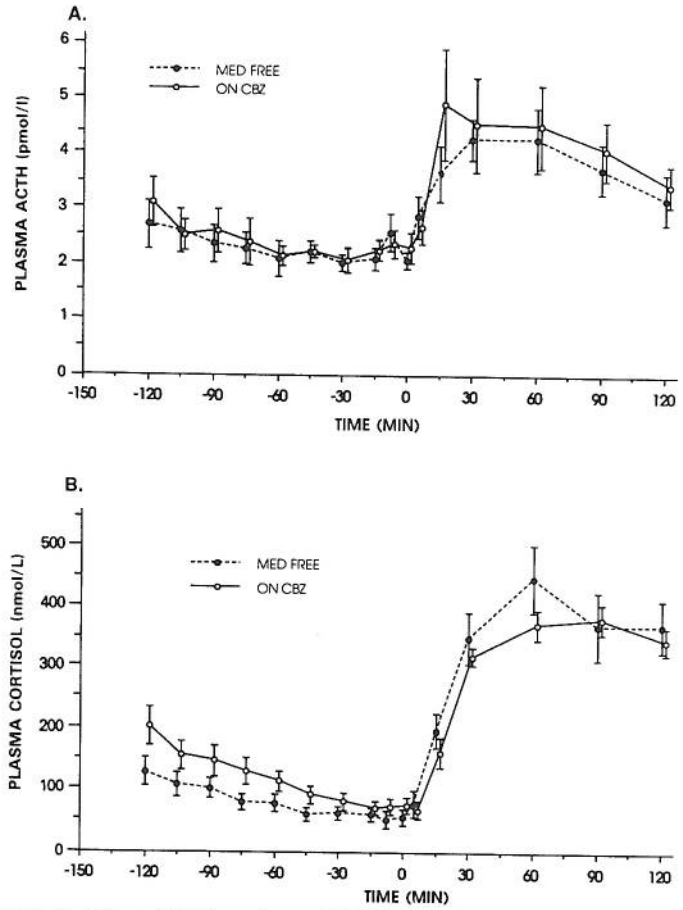

FIG. 2. Effect of CBZ on plasma ACTH (A) and cortisol (B) responses to ovine CRH in healthy volunteers (n = 9). CRH was given at a dose of 1 μg/kg by iv bolus at 2000 h. Each *point* represents the mean ± SEM.

under medication-free conditions (r = 0.75; $P < 0.05$) and a trend for a positive relationship between these parameters during CBZ treatment (r = 0.57; $P < 0.12$). Similarly, there was a significant positive correlation between the net integrated ACTH response to CRH and basal plasma cortisol in the medication-free state (r = 0.78; $P < 0.05$), but not during CBZ treatment (r = 0.44; $P < 0.2$).

Effect of CRH administration on CBG-binding capacity

During both the medication-free and CBZ treatment periods, the basal CBG-binding capacity had fallen significantly 60 min after CRH administration [from 433 ± 28 to 315 ± 25 nmol/L off CBZ ($P < 0.001$) and from 497 ± 36 to 342 ± 19 nmol/L on CBZ ($P < 0.001$); Fig. 5, A and B, respectively], at which time plasma cortisol levels tended to peak. The magnitude of this fall in CBG capacity during the course of the CRH stimulation test was significantly greater during the CBZ treatment

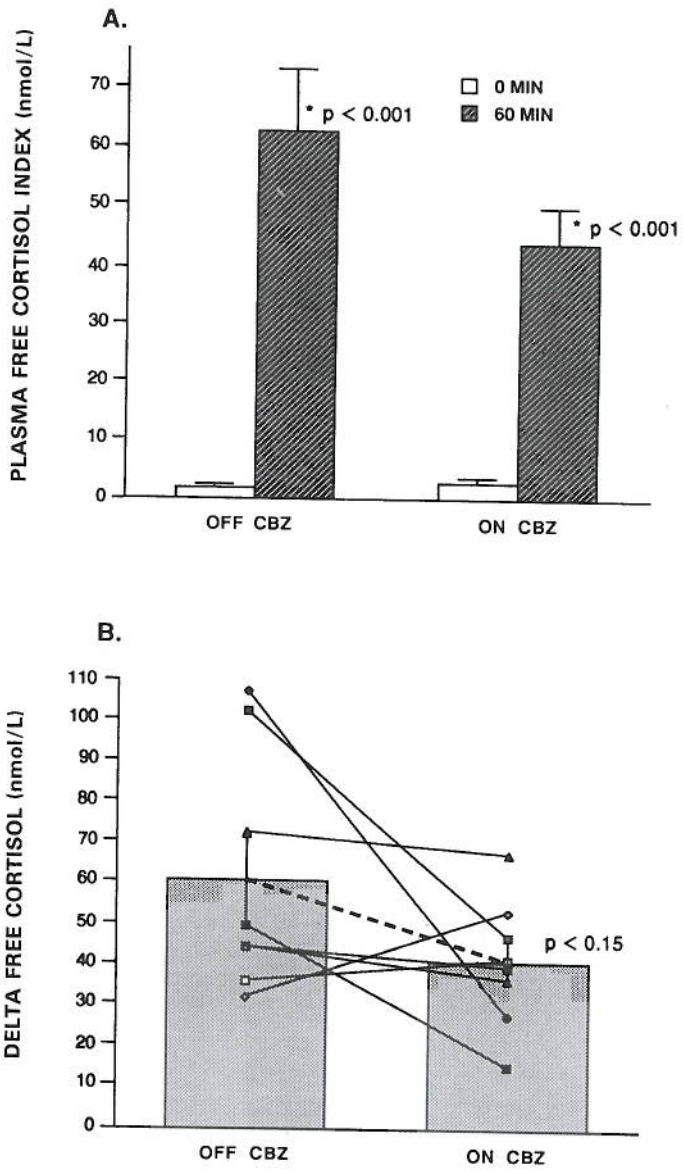

FIG. 3. A, Effect of CBZ on the plasma free cortisol index at baseline (0 min) and 60 min after CRH administration in healthy volunteers (n = 8). *Stars* indicate a significant difference between 60 and 0 min values off and on CBZ, respectively. B, Effect of CBZ on the response of the plasma free cortisol index to CRH in healthy volunteers (n = 8). DELTA FREE CORTISOL, represents the difference in the plasma free cortisol index. *Bars* represent the mean ± SEM.

period (−155 ± 22 *vs.* −118 ± 11 nmol/L; $P < 0.05$; Fig. 5C).

Plasma AVP and urinary osmolality

There was a trend toward a reduction in basal AVP levels during CBZ treatment compared to those in the drug-free state, at which time basal AVP levels were already near the detection limit of the assay (0.78 ± 0.69 on CBZ *vs.* 0.86 ± 0.31 pmol/L off CBZ; $P < 0.08$). Mean

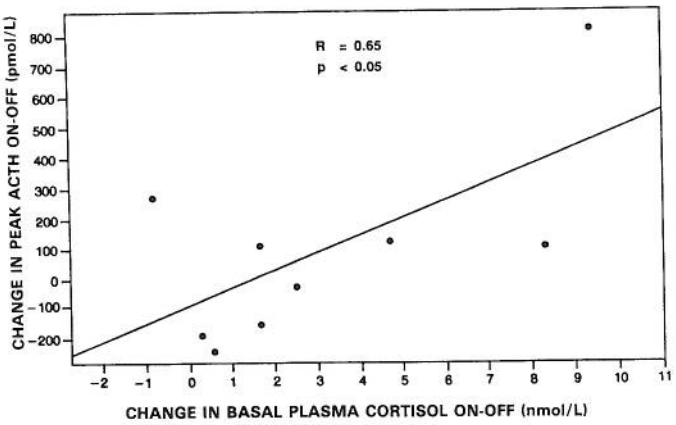

FIG. 4. Relationship between the change in the peak ACTH response to CRH and the change in basal plasma cortisol level during CBZ treatment in healthy volunteers (n = 9).

24-h urinary osmolality was significantly increased CBZ treatment (650 ± 105 *vs.* 525 ± 79 mmol/kg; $P < 0.05$).

Discussion

Basal ACTH and cortisol secretion

Mean 24-h UFC excretion and basal total plasma cortisol levels were significantly increased in healthy volunteers maintained on doses of CBZ producing plasma levels in the therapeutic range for anticonvulsant effects. The increased UFC excretion indicates an alteration in the overall set-point for cortisol secretion by CBZ in these healthy subjects. Our data are concordant with previous findings (2–4) showing increases in UFC and total plasma cortisol in CBZ-treated patients. Although the plasma free cortisol index was not significantly increased at 2000 h, we cannot exclude the possibility that plasma free cortisol may have been significantly elevated at an earlier time during the sampling period, when greater differences were observed in total plasma cortisol levels. CBZ did not significantly affect pre-CRH plasma ACTH levels in these subjects. The implications of this observation are discussed further below.

Effect of CBZ on plasma ACTH and cortisol responses to CRH and plasma AVP levels

There was a trend toward increased net integrated and peak ACTH responses, without a significant change in plasma total and free cortisol responses to CRH, during CBZ treatment. Given the CBZ-induced increase in UFC excretion, the lack of attenuation of ACTH responses to CRH implies an alteration by CBZ of pituitary responsiveness to CRH. Hence, we and others have shown that hypercortisolism in major depression and anorexia nervosa is associated with blunted ACTH responses to CRH (18, 19, 23–25), indicating that glucocorticoid negative feedback responsiveness is intact at the corticotroph and, thus, impaired at a suprapituitary level in these disorders. Hypercortisolism due to exogenous corticosteroid administration (26) and nonpituitary Cushing's syndrome (17) is also associated with attenuated or absent plasma

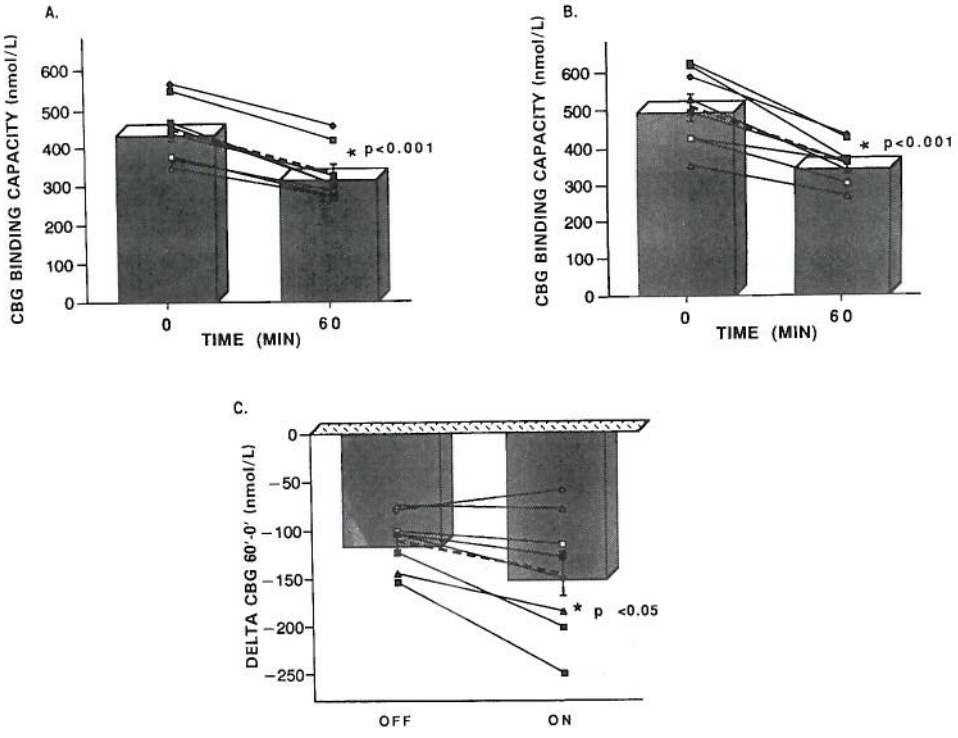

FIG. 5. Effect of CBZ on the change in plasma CBG-binding capacity associated with CRH administration in healthy volunteers (n = 8). A, Fall in CBG-binding capacity from baseline (0 min) to 60 min after CRH administration in volunteers studied while medication free. B, Fall in CBG-binding capacity after CRH administration in volunteers studied during the administration of CBZ. C, Effect of CBZ on the magnitude of fall in CBG-binding capacity observed during CRH administration. *Bars* represent the mean ± SEM.

ACTH responses to CRH. Therefore, the normal to elevated plasma ACTH responses to CRH during CBZ treatment in the present study may be seen as inappropriately robust given the subject's basal hypercortisolism.

The positive correlation between the CBZ-induced changes in basal cortisol levels and the ACTH responses to CRH further suggest that CBZ administration is associated with a relative inefficacy of glucocorticoid restraint at the pituitary corticotroph cell. To help account for such an effect, we speculate that CBZ may enhance corticotroph AVP receptor function and, thus, partially overcome glucocorticoid negative feedback at this level. Compatible with this hypothesis are data showing that CBZ enhances renal responsiveness to AVP (15) and decreases plasma sodium and osmolality in the context of subtle reductions in basal AVP secretion, as observed both in the present study and previously (27), and that AVP-induced ACTH secretion is less sensitive to glucocorticoid inhibition than that induced by CRH (12). Enhancement by CBZ of AVP action at the corticotroph would also account for our observation that CBZ did not increase evening basal plasma ACTH levels. Hence, pituitary-adrenal activity (and, thus, presumably endogenous CRH secretion) is lowest in the evening, and AVP is a weak ACTH secretagogue in the absence of CRH (12, 13). Thus, the robust ACTH responses to CRH on CBZ may represent the unmasking of an AVP-like action of CBZ through its synergistic action with the exogenously administered CRH, while the normal basal ACTH levels may reflect the lack of such synergism due to the low ambient CRH levels prevailing at this time of day. This idea is further supported by our preclinical findings that CBZ does not affect basal CRH secretion *in vitro*, actually blocks stimulated CRH secretion (5, 28), yet enhances ACTH secretion *in vitro* and *in vivo* (5). An alternative, although not necessarily incompatible, explanation for the latter effect of CBZ is an action on peripheral-type benzodiazepine receptors, which are known to be present in the anterior pituitary (29). Hence, CBZ has been shown to bind to these sites (30), while sharing with other such ligands the ability to stimulate pituitary ACTH secretion both *in vivo* and *in vitro* (5).

Although plasma cortisol responses to CRH were not significantly affected by CBZ, they were relatively attenuated compared with the ACTH responses. These data may reflect an effect of CBZ on adrenal responsivity to ACTH. The idea that such an effect could be mediated by peripheral-type benzodiazepine receptors is suggested by their presence at high concentrations in the adrenal cortex (29) and their localization within mitochondrial membranes (31, 32), where recent data indicate they play a critical role in the regulation of steroidogenesis (33).

The functional significance of the CBZ-induced increases in basal cortisol secretion and pituitary responsiveness to CRH is unknown. However, we note that a pituitary-driven increase in cortisol secretion would be expected to decrease basal hypothalamic CRH secretion, an effect that would add to the known inhibitory effect of CBZ on stimulated CRH secretion (5, 28). As CRH has been shown to exhibit proconvulsant properties in experimental animals (6), a reduction in central CRH secretion combined with the known anticonvulsant properties of moderately elevated cortisol concentrations (7, 8) may have an inhibitory effect on neuronal excitability and thereby increase the seizure threshold.

Effect of CRH administration on CBG-binding capacity

The CBG-binding capacity fell acutely after CRH administration, associated with the CRH-induced rise in plasma cortisol levels. This is compatible with previous preliminary data in healthy volunteers and patients with Cushing's disease (34). The basal CBG-binding capacity has also been shown to be reduced in various hypercortisolemic states (22, 35). Although the mechanism of this effect has not been definitively elucidated, it has been attributed to the effects of acute or chronic elevations in cortisol secretion, as CBG-binding capacity does not fall after CRH administration in patients with ectopic ACTH secretion (34), who do not show pituitary-adrenal responses to CRH (17, 34). Reduction of CBG-binding capacity with an acute rise in cortisol secretion may serve an adaptive function by rapidly increasing the availability of cortisol to target tissues during an acute emergency situation. The fall in CBG observed after CRH administration was accentuated during CBZ treatment. We cannot definitively account for this effect; however, we note that it occurred despite the lack of significant elevation of basal free cortisol at time zero or enhancement of the cortisol response to CRH. We, thus, speculate that CBZ may exert an effect on CBG regulatory mechanisms, which are independent of ambient cortisol concentrations.

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