Thyroid and Adrenal Dysfunction in Abstinent Alcoholic Men: Locus of Disturbance

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*Certain neuroendocrine abnormalities (e.g., blunted plasma adrenocorticotropic hormone [ACTH] response to corticotropin-releasing hormone [CRH] administration and blunted serum TSH response to thyrotropin-releasing hormone [TRH] administration) are common in alcoholic patients. It was the objective of this study to evaluate whether they are centrally mediated: that is, whether they are secondary to increased activity of CRH and/or TRH neurons. We evaluated the nocturnal secretion (2200 hours to 1000 hours, q 15 min) of plasma ACTH, serum cortisol, and serum TSH, and their responses to the combined administration of CRH and TRH, in 28 acutely abstinent alcoholic (age range: 32 to 57 years; mean: 42.4 years) and 19 normal men (age range: 21 to 52 years; mean: 32.1 years). To assess the validity of administering CRH and TRH simultaneously, we gave 10 additional abstinent alcoholic men (age range: 36 to 53 years; mean: 45.8 years), in random order and at least 4 days apart, either CRH, TRH, placebo, or CRH plus TRH. Nocturnal ACTH, cortisol, and TSH secretion, as well as cortisol and TSH responses after CRH plus TRH administration, were similar in alcoholic and normal men. However, ACTH peak responses to CRH plus TRH were reduced in the alcoholic men ($p < 0.05$). The ACTH, but not cortisol, response was greater after combined CRH plus TRH administration than after CRH alone ($p < .002$). The blunted ACTH response does not appear to be the result of increased endogenous CRH activity, because all parameters of nocturnal ACTH pulsatility were normal in the alcoholics. It rather appears to be secondary to an intrinsic defect in the CRH responsiveness of the pituitary corticotroph, possibly due to genetic vulnerability or to the toxic effects of prolonged alcohol abuse. **[Neuropsychopharmacology 9:255–266, 1993]***

KEY WORDS: *TRH, CRH, Thyroid hormones, Adrenal hormones, Alcoholism, Abstinence*

Chronic alcoholism is often associated with pseudo-Cushing's syndrome (Smals et al. 1976; Rees et al. 1977; van Thiel et al. 1983; Marks and Wright 1977) and euthyroid sick syndrome (Loosen et al. 1979, 1983, 1992). There are abnormalities in hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axes function that characterize these syndromes, such as, increased plasma cortisol concentration (Valimaki et al. 1984; Risher-Flowers et al. 1988; Mendelson and Stein 1966), resistance of plasma cortisol to suppression by dexamethasone (Swartz and Dunner 1984; Targum 1984), blunted plasma adrenocorticotropic hormone (ACTH) response to corticotropin-releasing hormone (CRH) administration (Adinoff et al. 1990; von Bardeleben et al. 1989; Heuser et al. 1988; Loosen et al. 1991), and blunted serum TSH response to thyrotropin-releas-

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ing hormone (TRH) administration (Loosen et al. 1979, 1983, 1992; Loosen 1988).

It has been postulated that these functional alterations in the HPA and HPT axes are centrally mediated; that is, they are secondary to increased activity of CRH and/or TRH neurons, resulting in downregulation of CRH and TRH receptors (Loosen 1988; Adinoff et al. 1990; von Bardeleben et al. 1989; Loosen et al. 1991, 1992; Holsboer et al. 1987). In support of this concept, Mortola et al. (1987) demonstrated that the hypercortisolemia in women with major depressive disorder was associated with increased ACTH pulse frequency, expanded cortisol secretory episodes, and a shortened evening quiescent period of cortisol secretion, suggesting a centrally mediated HPA axis activation. To test this hypothesis in alcoholic patients, we studied the nocturnal secretory patterns of immunoreactive plasma ACTH, serum cortisol, and serum TSH and their responses to CRH and TRH. Hypothesizing that increased release of CRH and TRH is associated with increased activity of the endogenous pulse generator(s), we utilized a computer-assisted pulse-analysis program (CLUSTER) to determine the parameters of nocturnal hormonal pulsatility.

SUBJECTS AND METHODS

Subjects

Twenty eight alcoholic men, aged 32 to 57 years (42.4 ± 7.6 years, mean ± SD), were recruited from the Nashville Veterans Administration Chemical Dependency Treatment Program (VA-CDTP) and studied after they had given their informed consent. All had drunk heavily, leading to multiple alcohol-related hospital admissions. At the time of study, they were abstinent from alcohol for 15 days to 110 days (Table 1) and were taking no psychotropic medication. Abstinence was assured by participation in the inpatient VA-CDTP. Nineteen normal volunteer men, aged 21 to 52 years (32.1 ± 6.2 years) were also studied. Diagnoses were made according to the research diagnostic criteria (RDC)(Spitzer et al. 1978), the Diagnostic and Statistical Manual of Mental Disorders (DSMIII-R), and the Michigan Alcoholism Screening Test (Selzer 1971); all alcoholic patients met RDC requirements for definite alcoholism and DSMIII-R criteria for alcohol dependence. Twenty-six of the alcoholic men also fulfilled criteria for type 2 alcoholism according to Cloninger (1987), with onset of drinking before age 25, development of spontaneous alcohol-seeking behavior or inability to abstain, frequent fighting and arrests when drinking, infrequent psychological dependence with loss of control, infrequent guilt and fear about alcohol dependence, and the triad (characteristic for antisocial personality disorders) of high novelty seeking, low harm avoidance, and low reward dependence. Two patients were classified as type 1 alcoholics. Medical illness was excluded by normal history, physical examination, and routine screening laboratory tests. A complete liver profile was also obtained immediately before study entry (Table 2). Seven alcoholic men had gamma-glutamyltransferase elevations (Table 2) consistent with the long-standing nature and severity of their alcoholism (Table 1). None of the alcoholic or normal men was clinically depressed at the time of testing, as assessed by clinical interview and the Hamilton Depression Rating Scale (Hamilton 1960); the score (items 1 to 17) was less than 8 in all men. An additional 10 alcoholic men, aged 36 to 53 years (45.8 ± 6.4 years), were also studied to validate administering CRH plus TRH simultaneously. They received, in random order and at least 4 days apart, either CRH, TRH, placebo, or CRH plus TRH.

Table 1. Clinical Characteristics of the Abstinent Alcoholic Men

		Alcoholism			
Subjects	Age (yrs)	Psych.[a] History	History (yrs)	MAST[b] (score)	Abstinence (days)
1	35	MDD, PD	21	30	39
2	56	–	40	10	16
3	35	–	25	29	23
4	32	–	16	29	21
5	57	–	4	29	19
6	36	–	8	23	21
7	48	–	33	25	22
8	42	–	25	26	20
9	41	–	20	29	15
10	35	–	20	14	29
11	37	MDD	28	29	90
12	33	–	17	17	53
13	46	MDD	30	24	34
14	36	MDD, PDA	21	12	49
15	57	–	30	24	110
16	45	PDA	30	29	37
17	44	PDA	28	27	36
18	50	MDD, PD	30	27	30
19	32	MDD, PDA	10	27	32
20	40	PDA	20	27	69
21	43	–	28	12	33
22	52	MDD	30	27	61
23	36	MDD, PDA	21	27	60
24	45	MDD, PDA	29	29	30
25	39	PDA	21	29	45
26	48	–	32	29	60
27	49	MDD	31	29	107
28	38	PDA	20	27	39
Mean ± SD	42.4 ± 7.6	–	23.3 ± 8.1	24.8 ± 5.9	42.9 ± 25.7

[a] Past psychiatric disorders: MDD, major depressive disorder; PD, panic disorder; PDA, polydrug abuse (i.e., alcoholism plus cannabis, cocaine, or opiate dependence).
[b] The Michigan Alcoholism Screening Test (Selzer 1971).

Table 2. Liver Profiles of Abstinent Alcoholic Men

Subjects	Albumin[a]	LDH[b]	Alkaline[c] Phosphatase	Total[d] Protein	AST[e]	γ-GT[f]
1	4.1	82	12	6.2	12	9
2	3.8	115	16	6.8	13	22
3	4.2	105	12	6.9	8	13
4	3.9	88	10	6.0	12	8
5	4.1	91	10	6.6	17	24
6	4.3	106	7	6.7	13	28
7	3.9	98	9	6.7	26	71*
8	4.1	42	16	6.4	12	15
9	4.1	113	7	7.1	14	34
10	4.3	104	6	7.2	12	32
11	4.3	135	5	6.9	15	6
12	4.4	95	9	7.0	10	10
13	4.0	91	9	6.2	8	6
14	3.9	113	9	6.7	9	12
15	4.0	66	11	6.5	9	43*
16	4.3	121	6	7.1	14	15
17	3.9	236	–	7.8	23	5
18	4.7	112	10	7.7	57	60*
19	4.6	129	64	8.1	27	23
20	4.2	106	10	6.8	16	19
21	4.0	116	6	6.8	7	4
22	3.9	145	6	6.5	18	6
23	4.4	93	10	7.0	19	41*
24	4.5	93	9	7.0	20	77*
25	4.1	103	9	6.7	12	37
26	4.4	84	11	7.1	8	41*
27	4.3	138	6	7.5	11	19
28	4.1	127	11	7.1	56	72*
Mean	4.2	109	11.3	6.9	17.1	26.9
± SD	0.2	33	10.9	0.5	12.3	21.6

[a] Normal range: 3.5 to 5.0 gr/dL.
[b] Normal range: 125 to 250 IU/L.
[c] Normal range: 2 to 40 IU/L.
[d] Normal range: 6 to 8 gr/dL.
[e] Aspartate aminotransferase = SGOT (normal range: 4 to 40 IU/L).
[f] γ-glutamyltransferase (normal range: 2 to 40 IU/L).

Hormone Testing

The alcoholic and normal men were admitted to the General Clinical Research Center (GCRC) of Vanderbilt University Medical Center for 2 days. A standardized activity schedule was maintained with meals at 0800 hours, 1200 hours, and 1700 hours, and lights out at 2300 hours. Meals contained approximately 50% carbohydrate, 35% fat, and 15% protein. Ambulation and daytime napping were minimized.

Nocturnal Hormone Secretion. At 2000 hours on the first day an intravenous line was inserted, and, beginning at 2200 hours, blood samples were drawn every 15 minutes for 12 hours.

Releasing Hormone Administration. At 1600 hours the following day, synthetic ovine CRH (1 μg/kg) and TRH (200 μg) were administered as sequential 20-second infusions, at least 1 hour after an intravenous heparin lock was placed in a forearm vein (Sheldon et al. 1985). Blood samples were withdrawn 15 minutes before, just prior to, and 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the infusion.

Separate Administration of CRH, TRH, CRH plus TRH, and Placebo. The validity of simultaneously administering CRH plus TRH has been demonstrated in normal subjects (Sheldon et al. 1985; Cohen et al. 1986; Holl et al. 1988; Schopohl et al. 1986) but not in alcoholic subjects. Therefore, we studied 10 additional alcoholic men, using the same study design for peptide dosage and time of administration. Each patient received, in random order and at least 4 days apart, CRH alone, TRH alone, CRH plus TRH, or placebo.

Hormone Assays

Ethylenediaminetetraacetic acid plasma and serum were prepared and stored at −70°C for later assay.

Plasma ACTH and serum cortisol and TSH were measured by radioimmunoassay. The assay for plasma ACTH employed rabbit anticorticotropin serum IgG-ACTH-1 (IgG Corp., Nashville, TN), which is directed at the bioactive ACTH-(5-18) sequence. Synthetic human ACTH (Ciba-Geigy, Basle, Switzerland) was used as ^{125}I-labeled tracer and as reference standard. Phase separation was achieved by the addition of goat anti-rabbit IgG. Sensitivity of the ACTH assay was 1.1 to 2.2 pmol/L. Serum TSH, free thyroxine (FT4), and total triiodothyronine (QT3) concentrations were measured with commercially available kits. All radioimmunoassay methods have previously been described (Sheldon et al. 1985). All hormone concentrations are given in SI units (Lundberg et al. 1986).

Pulse Analysis

A computer-assisted pulse-analysis program (CLUSTER) was used to evaluate pulse frequency and amplitude, interpulse interval, and area-under-the-curve of nocturnal hormone secretion. Significant pulses were detected with Veldhuis et al.'s modification (Veldhuis et al. 1984; Urban et al. 1989) of the method of Santen and Bardin (1973), which requires that a significant pulse exhibit a nadir-to-peak difference of at least four times the intraassay coefficient of variation at the level of the nadir. The intraassay coefficient of variation for any one subject was computed from 30 to 90 assay replicates of a serum pool derived from that individual's samples and run in the same assay. For TSH and cortisol, nadir and peak sizes of 1 were used, with a t-statistic of 2.0 for both upstroke and downstroke, whereas for ACTH a nadir size of 2 and a peak size of 1 were used, with a t-value of 2.0 for both upstroke and downstroke (J. Veldhuis, personal communication). For all hormones, a power function was used to estimate variance.

To evaluate possible associations between alterations in the basal nocturnal rhythm and the pattern of response to CRH plus TRH administration, we correlated the plasma ACTH, serum cortisol, and serum TSH response increments to the releasing hormones with their peak pulse frequency and peak pulse amplitude.

Statistical Analysis

Nocturnal and response data across groups were analyzed by repeated-measures analysis of variance (ANOVA) (Winer 1976). For the nocturnal hormone levels, group (control vs. alcoholic) was a between-subjects factor, and time was a within-subjects factor. For the hormone response test, a similar design was used except that the levels for the time factor were baseline versus peak values. Results from the CLUSTER analysis were analyzed using a one-way ANOVA, with group as a between-subjects factor. Pearson's Product Moment Correlation was used for the correlation analyses of nocturnal and response data. For all analyses, an alpha level of 0.01 was used to control for the number of hormones (five) being analyzed.

RESULTS

Nocturnal Hormonal Secretion

Plasma ACTH (Fig. 1) and serum cortisol concentrations increased significantly ($p < .0001$) during the night in both alcoholic and normal men; there were no intergroup or time-by-group interactions. The CLUSTER analysis showed that the pulse frequency and amplitude of ACTH, cortisol, and TSH secretion were similar in alcoholic and normal men (Table 3).

Responses to CRH plus TRH Administration

The increment (peak minus baseline) and area-under-the-curve above baseline were calculated for plasma ACTH, serum cortisol, and serum TSH. There were no significant differences in cortisol or TSH responses been alcoholic and normal men (Table 4). In contrast, repeated-measures ANOVA revealed a significant time-by-group effect for ACTH ($F = 4.32$; $df = 1,45$; $p = .045$) (Table 4). Although ACTH responses to CRH were reduced in the alcoholic men, the resulting plasma ACTH concentrations stimulated normal serum cortisol concentrations (Fig. 2).

Correlation Between Nocturnal Secretion and Response to Releasing Hormones

There was no significant correlation between the increment in plasma/serum hormone concentration after CRH plus TRH administration and either nocturnal peak frequency or nocturnal peak amplitude.

Separate Administration of CRH, TRH, CRH plus TRH, and Placebo

The responses of serum cortisol and TSH were unaffected by the combined administration of CRH plus TRH. However, the ACTH response was greater after CRH plus TRH than after CRH alone ($F = 19.12$; $df = 1,9$; $p < .002$) (Fig. 3).

DISCUSSION

Adrenal Hormones

Under basal conditions, the HPA axis is most active at approximately the time of awakening. Thereafter,

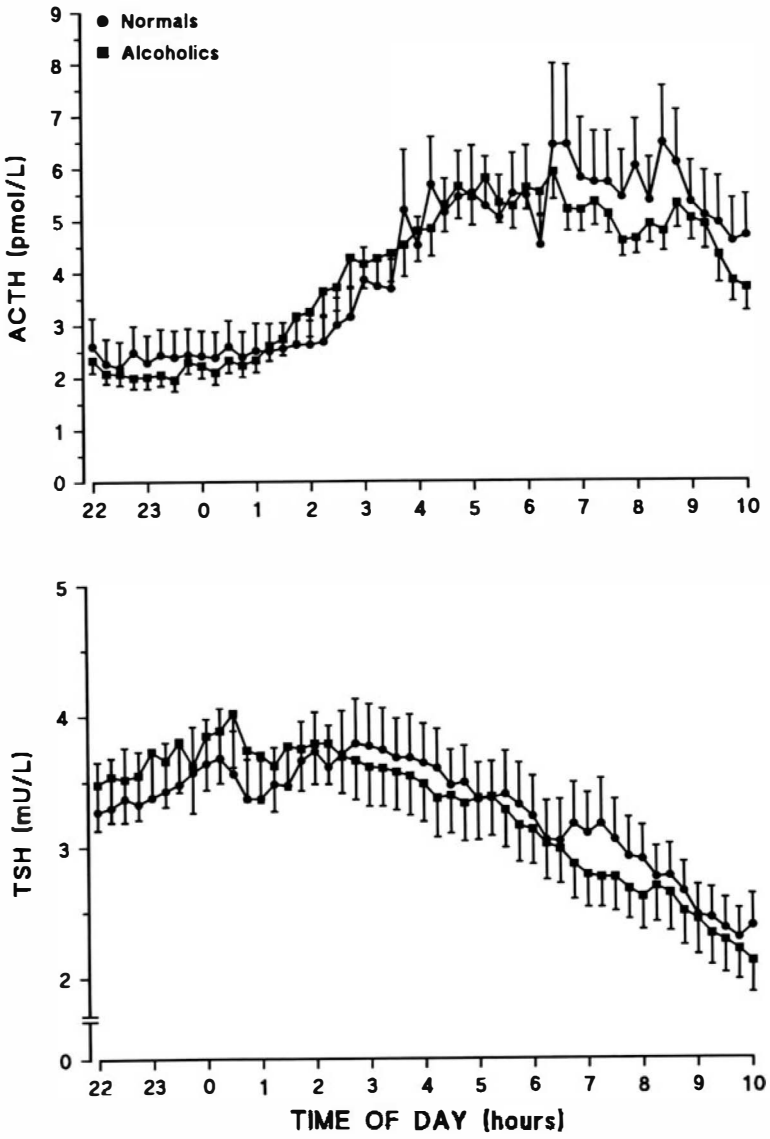

Figure 1. Nocturnal secretion of plasma ACTH and serum TSH in 28 alcoholic and 19 normal men.

Table 3. CLUSTER Analysis of the Nocturnal Hormonal Concentrations in 28 Abstinent Alcoholic and 19 Normal Men

Hormones	Peaks/12 Hours	Peak Amplitude (%)	p^a
ACTH (pmol/L):			
Alcoholics	4.6 ± 1.2	217 ± 52	NS[b]
Controls	4.1 ± 1.2	293 ± 227	
Cortisol (nmol/L):			
Alcoholics	5.2 ± 1.8	342 ± 142	NS
Controls	5.7 ± 1.8	338 ± 152	
TSH (mU/L):			
Alcoholics	4.1 ± 2.0	131 ± 16	NS
Controls	3.3 ± 1.8	134 ± 15	

[a] Repeated-Measures ANOVA.
[b] Alcoholics not significantly different ($p < .05$) from controls.
Data are presented as means ± SD.

Table 4. Hormonal Responses After CRH/TRH Administration in 28 Abstinent Alcoholic and 19 Normal Men

Hormones	Baseline	Peak	AUC	p^a
ACTH (pmol/L):				
Alcoholics	3.3 ± 1.7	9.9 ± 4.4	814 ± 338	<0.0001[b]
Controls	4.1 ± 3.0	13.7 ± 7.4	1046 ± 529	<0.05[c]
Cortisol (nmol/L):				
Alcoholics	230 ± 98	590 ± 128	59,450 ± 10,910	<0.0001[b]
Controls	208 ± 83	618 ± 168	59,230 ± 14,250	
TSH (mU/L):				
Alcoholics	2.4 ± 1.7	23.7 ± 9.6	1839 ± 760	<0.0001[b]
Controls	2.3 ± 1.0	20.5 ± 7.7	1676 ± 717	

[a] Repeated-measures ANOVA.
[b] Increment (peak minus baseline) in hormone concentration for both alcoholics and controls.
[c] Alcoholic versus control increment in hormone concentration.
Data are presented as means ± SD.

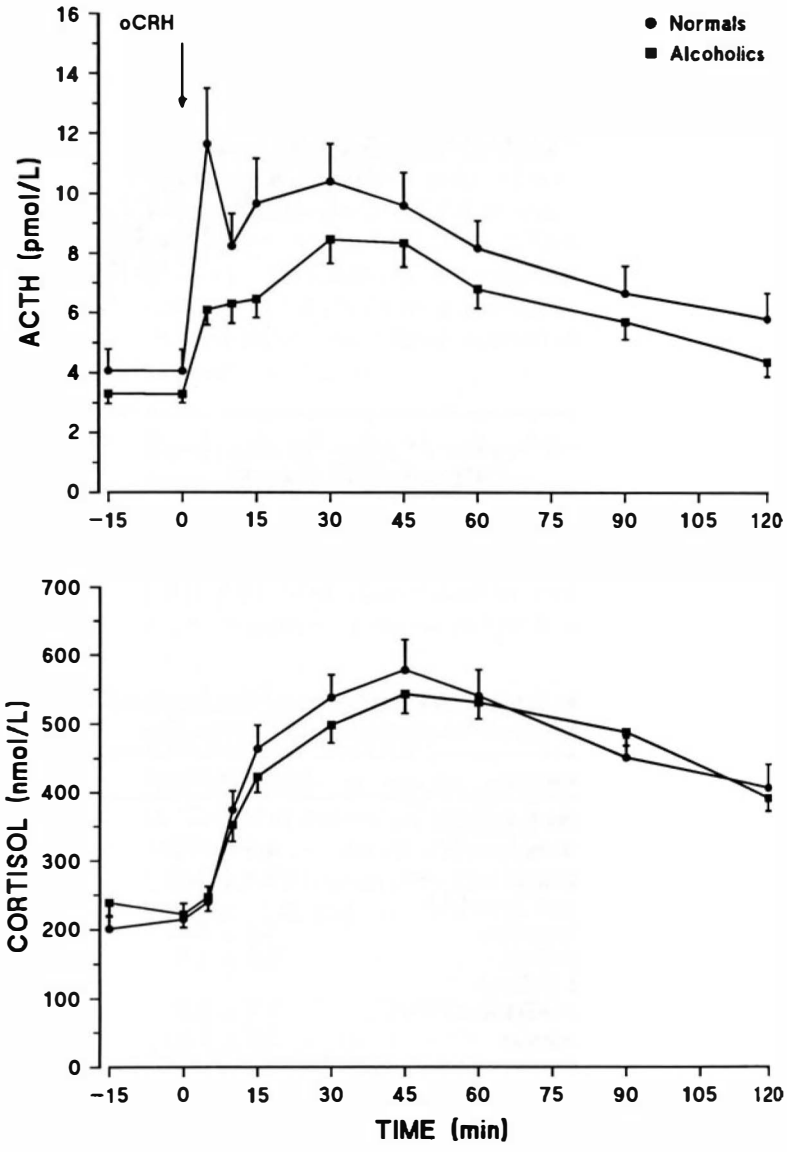

Figure 2. Responses of plasma ACTH and serum cortisol to CRH administration in 28 alcoholic and 19 normal men. Repeated-measures ANOVA revealed significant time × group effects for ACTH ($F = 4.32$, $df = 1,45$; $p = .045$).

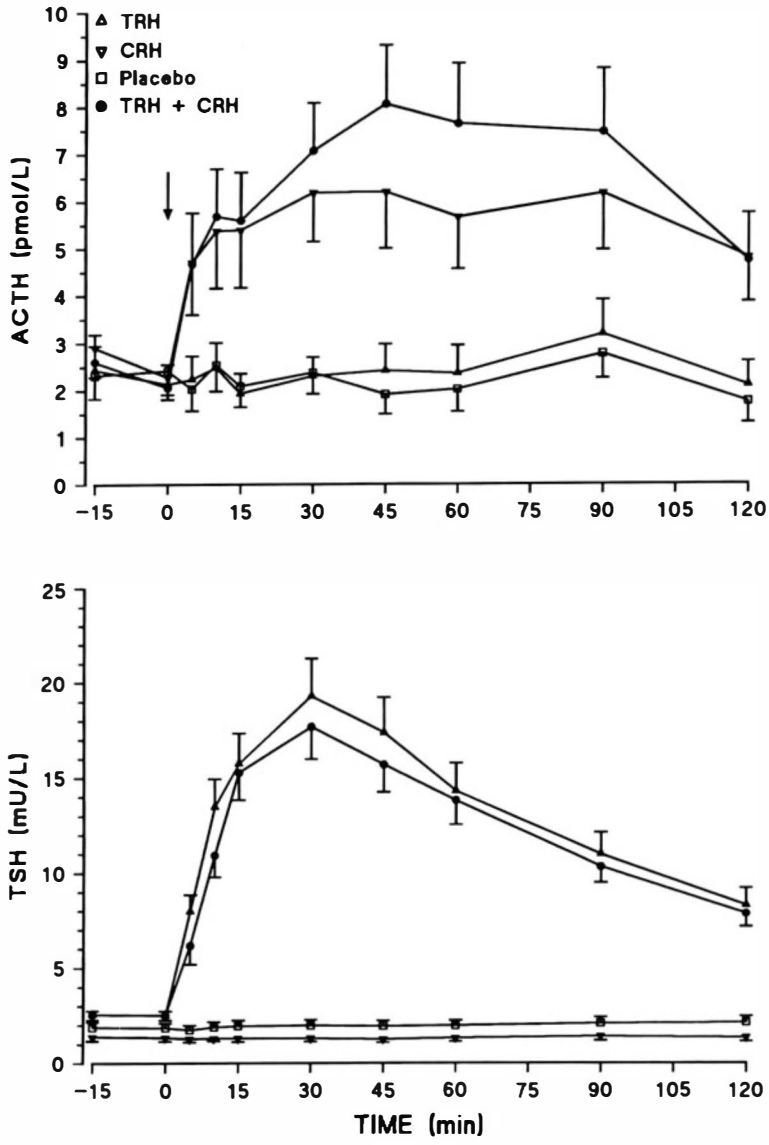

Figure 3. Responses of plasma ACTH and serum TSH to the separate administration of TRH, CRH, placebo, and TRH plus CRH in 10 alcoholic men. Repeated-measures ANOVA revealed that the ACTH response was greater after CRH plus TRH than after CRH alone ($F = 19.12$; $df = 1,9$; $p < .002$).

plasma ACTH and serum cortisol concentrations progressively decrease to reach nadirs during the early hours of sleep (Little 1981). Our results indicate that nocturnal secretion of ACTH and cortisol is normal in abstinent alcoholic men: mean hormone concentration, as well as peak frequency, peak amplitude, and total area-under-the-curve were similar in alcoholic and normal men. This finding is consistent with most previous reports. In a study of the acute and chronic effects of alcohol in normal volunteers, Prinz et al. (1980) reported no change in nocturnal plasma cortisol concentrations, as did Bertello et al. (1982) in alcoholic men with hypogonadal features. Rosman et al. (1982) noted normal mean 24-hour total and free-plasma cortisol concentrations and normal circadian rhythmicity, but decreased circadian amplitude and fewer cortisol secretory peaks in patients with alcoholic liver disease. In contrast, Iranmanesh et al. (1989) reported elevated mean and total integrated 24-hour serum cortisol concentration, normal cortisol pulse frequency, increased circadian amplitude, and delay of the circadian peak during acute abstinence; sustained abstinence was associated with decreased mean maximal peak amplitude and mean 24-hour concentrations of serum cortisol. Nocturnal ACTH secretion has not previously been studied.

Like other investigators, we noted significantly attenuated plasma ACTH responses to CRH in the alcoholic men that were, nevertheless, apparently sufficient to stimulate normal serum cortisol responses. This presumably reflected the fact that the plasma ACTH concentrations were acutely near-maximally stimulating for the adrenal cortex. Alternatively, it could reflect increased adrenocortical sensitivity to ACTH in alcoholic

patients. Berman et al. (1990) reported blunted ACTH but normal cortisol responses after insulin-induced hypoglycemia in actively drinking alcoholic patients. Adinoff et al. (1990) demonstrated significantly attenuated ACTH but normal cortisol responses in alcoholics at both 1 and 3 weeks of abstinence. Von Bardeleben et al. (1989) reported blunted ACTH responses in alcoholic patients during acute withdrawal and after 2 to 6 weeks and 2 to 6 months of abstinence. The data suggest that the blunted ACTH response to CRH remains stable over time and, consequently, that acute alcohol intake and/or withdrawal phenomena are unlikely contributors to the ACTH blunting. Between 19% and 39% of nondepressed alcoholic patients show resistance to dexamethasone suppression during alcohol withdrawal; this rate drops to 6% to 18% after approximately 3 weeks of abstinence (Khan et al. 1984; Evans and Golden 1987). It is unclear why the blunted ACTH response to CRH in abstinent alcoholic patients persists over time, whereas resistance to dexamethasone suppression does not.

In an additional 10 alcoholic men whom we studied, the ACTH response after CRH plus TRH administration was significantly greater than after CRH alone. Although the pathophysiology of this finding remains to be determined, the data suggest that the combined use of TRH and CRH may produce some false positive ACTH responses, making the ACTH responses to CRH of our alcoholic patients appear less blunted than was actually the case. Previous studies in normal healthy volunteers had shown that ACTH after the combined administration of CRH plus TRH was comparable to that after separate administration (Sheldon et al. 1985; Cohen et al. 1986; Holl et al. 1988; Schopohl et al. 1986).

Blunted ACTH responses to CRH are not specific for alcoholism. They have also been observed in patients with anorexia nervosa (Gold et al. 1986a; Hotta et al. 1986), panic disorder (Roy Byrne et al. 1986), major depression (Gold et al. 1986b; Lesch et al. 1989; Kathol et al. 1989; Amsterdam et al. 1988; Holsboer et al. 1984), and posttraumatic stress disorder (Smith et al. 1989). However, in each of these conditions, ACTH blunting is usually associated with demonstrable hypercortisolemia, whereas the alcoholic patients reported here had normal basal serum cortisol levels. It is possible that their total daily cortisol secretion may have been increased, but this was not reflected in serum cortisol concentrations during the observation period.

It has been postulated that the blunted ACTH response to CRH in depression (Gold et al. 1986b; Lesch et al. 1989; Kathol et al. 1989; Amsterdam et al. 1988; Holsboer et al. 1984) and alcoholism (Holsboer et al. 1987) are the result of hypothalamic dysfunction, that is, increased activity of CRH neurons. In support of this concept, Mortola et al. (1987) demonstrated that the hypercortisolemia in women with major depressive disorder was associated with increased ACTH pulse frequency, expanded cortisol secretory episodes, and a shortened evening quiescent period of cortisol secretion, suggesting a centrally mediated HPA axis activation. However, the blunted ACTH response in depression may be a direct effect of basal hypercortisolemia, because acutely lowering cortisol secretion by metyrapone administration restores ACTH responses to CRH to normal (von Bardeleben et al. 1988). In our alcoholic patients, nocturnal ACTH pulse frequency and amplitude were normal, suggesting that the blunted ACTH response to CRH was not due to increased secretion of endogenous CRH.

Adinoff et al. (1990) have suggested that the blunted ACTH response in alcoholic patients reflects an intrinsic defect in the pituitary corticotroph's response to CRH, possibly due to genetic vulnerability or to the toxic effects of prolonged alcohol abuse. Our results are consistent with this hypothesis or with an effect of brief abstinence from alcoholism, but they provide no further insights into etiology, pathophysiology, or (in the case of toxicity) persistence over time.

The finding of blunted ACTH responses in abstinent alcoholics suggests that the abnormality may be a trait marker, at least in some patients. Although the psychiatric manifestations of chronic alcohol abuse usually return to normal after a short period of abstinence, other changes, including neuroendocrine reactivity (Loosen et al. 1983, 1991; Adinoff et al. 1990; von Bardeleben et al. 1989; Heuser et al. 1988), event-related brain potentials (Begleiter et al. 1981), and cognitive behavior (Tarter and Edwards 1985; Eckardt and Ryback 1981) may remain impaired for several months to years after abstinence and may even be seen in the nonalcoholic sons of alcoholic patients (Begleiter et al. 1984; Tarter et al. 1984). Moreover, Schuckit et al. (1987a, 1987b, 1988) demonstrated in a series of elegant experiments that sons of alcoholic fathers had lower levels of ACTH, cortisol, and prolactin following an ethanol challenge, suggesting that these neuroendocrine abnormalities may be part of a genetic predisposition toward alcoholism. A more detailed analysis of both alcoholic patients (studied at various times during abstinence from alcoholism) and sons of alcoholics is necessary to document whether blunted ACTH response to CRH can be added to the increasing list of abnormalities seen in these individuals.

Thyroid Hormones

Under basal conditions, the HPT axis is most active during the late evening hours, after which time, serum TSH levels decrease steadily to reach a nadir during the early morning hours (Ingbar 1985). Our results indicate that nocturnal TSH secretion, including its peak frequency, peak amplitude, and total area-under-the-curve, is normal in acutely abstinent alcoholic men.

The TSH response to CRH plus TRH was also normal in our alcoholic patients. These results are at variance with most reports in the literature, including our own (Loosen et al. 1979, 1983, 1990), which demonstrated blunted TSH responses in some alcoholic men both during acute withdrawal and after prolonged abstinence (Loosen et al. 1992; Loosen 1988). It was possible that the combined administration of CRH and TRH may have produced false-positive TSH responses, but our study of 10 additional alcoholic men indicated that this was not the case. Differences in patient population characteristics may account for the divergent findings. Most of our patients suffered from severe, early onset, type II alcoholism (Cloninger 1987). A direct comparison of type I and type II alcoholics is necessary to support or reject this possibility. It is also possible that, because of early onset and disease severity, our patients suffered from liver disease. This is supported by gamma-glutamyltransferase elevations, which are reported to correlate with resistance to dexamethasone suppression. A recent review of the literature (Loosen et al. 1992) revealed that TSH blunting is more common in alcoholics without liver disease than in those with liver disease. Nine studies (Loosen et al. 1983; Dackis et al. 1984; Casacchia et al. 1985; Agner et al. 1986; Radouco-Thomas et al. 1984; Marchesi et al. 1989; Mueller et al. 1989; Willenbring et al. 1990; Garbutt et al. 1991) evaluated the TSH response to TRH in abstinent alcoholics without liver disease, and all but one (Agner et al. 1986) reported a blunted TSH response (Usually defined as a TSH increment of <5 or <7 mU/L) to TRH in some patients. In all, 163 patients received TRH, of whom 43 (26%) showed a blunted TSH response. Six studies (van Thiel et al. 1979; Chopra et al. 1974; Agner et al. 1986; Monza et al. 1981; Hasselbalch et al. 1981; Green et al. 1977) evaluated abstinent alcoholics with liver disease, and all but one (Green et al. 1977) reported normal TSH responses. However, elevated basal serum TSH (van Thiel et al. 1979; Monza et al. 1981; Nomura et al. 1975; Green et al. 1977; Chopra et al. 1974) and reduced basal serum QT3 levels (van Thiel et al. 1979; Nomura et al. 1975; Green et al. 1977; Chopra et al. 1974; Israel et al. 1979; Hepner and Chopra 1979) were rather common. The reductions in serum QT3 concentrations appeared to derive from decreased conversion of T4 to T3, which was thought to be due to liver cell damage with loss of deiodinating capacity. Israel et al. (1979) and Israel and Orrego (1984) observed a strong inverse correlation between an index of liver disease and serum QT3 levels and reported that increasing QT3 levels during hospitalization were associated with clinical improvement. In our patients, in contrast, basal serum TSH and QT3 concentrations and TSH responses to TRH were all normal. More studies of abstinent alcoholics, especially ones that carefully control for the effects of liver status on thyroid function, will be required to explain the reason for the different findings of various investigators.

In summary, we observed no abnormalities in HPA or HPT function in abstinent alcoholic men other than a blunted ACTH but normal cortisol response to CRH. The blunted ACTH response does not appear to be the result of increased endogenous CRH activity, because all parameters of nocturnal ACTH pulsatility were normal in the alcoholics; rather, it may be due to a genetic defect or the effect of prolonged alcohol abuse or brief abstinence from chronic alcoholism.

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