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Dexamethasone and Adrenocorticotropin Suppress Prolactin Secretion in Humans

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It has been demonstrated that the regulatory pathways mediating basal and/or stimulus-induced prolactin (PRL) release in mammals are highly sensitive to adrenal corticoid inhibitory influence. We have investigated the effect of four different doses of dexamethasone (DEX) and the effect of adrenocorticotropin on PRL secretion in 197 patients (169 female, 28 male; age: 18–66 yr) with suspected hypercortisolemia—but only those with a normal glucocorticoid suppression test were involved in the study—and in 66 female patients (age: 18–39 yr) with suspected adrenocorticotropin-dependent hyperandrogenism. Overnight (1 mg), low-dose (0.5 mg every 6 h for 2 d), high-dose (2 mg every 6 h for 2 d), and long-lasting administration of DEX (0.5 mg every 6 h for 5 d) resulted in a significant decrease in PRL levels compared to the baseline. Similarly, a reduction in PRL levels could be detected following injection of adrenocorticotropin (250 µg). In hyperprolactinemic patients, the DEX-induced increase in PRL (ΔPRL, expressed in percentage of baseline) was significantly larger compared with normoprolactinemic subjects in all groups except those who received high-dose DEX) or adrenocorticotropin. These data clearly indicate that the secretory function of PRL cells in humans is sensitive to changes in the activity of the hypothalamo-pituitary-adrenal axis in a dose-dependent manner.

Key Words: Adrenocorticotropin; adrenal corticoid; prolactin; dexamethasone.

Introduction

The functional relationships between glucocorticoids and pituitary prolactin (PRL) secretion are widely studied in mammals *(1)*. It has been shown in rats that both the basal and stress-induced plasma levels of PRL significantly increase after adrenalectomy *(2)*, whereas the effects of adrenalectomy can be reversed by the substitution of corticosteroids *(3,4)*. Similarly, adrenalectomy enhances whereas exogenous glucocorticoid (dexamethasone [DEX] treatment) suppresses the secretory responses of PRL provoked by different stimuli, such as hypoglycemia *(5)*, administration of estrogen *(6)*, immobilization *(7)*, psychologic stresses and footshock *(8)*, as well as during suckling stimulus *(9)* or following treatment with thyrotropin-releasing hormone (TRH) *(10)*. Moreover, pharmacologic blockade of glucocorticoid receptors with mifepristone (RU486) enhances some of the aforementioned stimuli-induced PRL release *(11)*. In addition, long-term elevation of the serum glucocorticoid level induced by chronic administration of adrenocorticotropin (adrenocorticotropic hormone [ACTH]) *(12)* or hydrocortisone *(13)*, as well as prolonged stress *(14)*, results in a decrease in opioid-induced PRL secretion.

Parallel to the animal experiments, significantly elevated basal levels of plasma PRL and an enhanced PRL response to TRH have been found in hypocortisolemic (Addison's disease) patients compared with normocortisolemic subjects *(15,16)*. Similar changes could be detected in isolated ACTH deficiency *(17)*, whereas, high-dose of glucocorticoid therapy results in a lower mean PRL level *(16)* and a decrease in PRL response to TRH *(17)*. DEX suppression test is commonly used in patients with depression *(18)* to characterize the potential variants of major depressive disorders. In these studies, an inverse PRL response was seen in endogenous depression compared to normal as well as in patients suffering from exogenous depression *(19)*. Moreover, the suppressive effect of DEX on PRL levels was more pronounced in healthy control subjects and in patients with nonendogenous depression than in those with endogenous depression *(20)*. It has also been demonstrated that low-dose of DEX (0.5 mg) results in greater PRL suppression in combat-exposed veterans either with or without posttraumatic stress disorders than in healthy subjects *(21)*. DEX (1 mg) significantly enhances the meal-induced elevation of plasma PRL in both bulimic and healthy women *(22)*. Furthermore, it has been shown that DEX (2 mg every 6 h for 5 d) treatment results in a reduction in PRL response to TRH in both healthy women *(23)* and men *(24)*. By contrast, others found that daily injection of 16 mg of DEX for 3 d did not cause any change in

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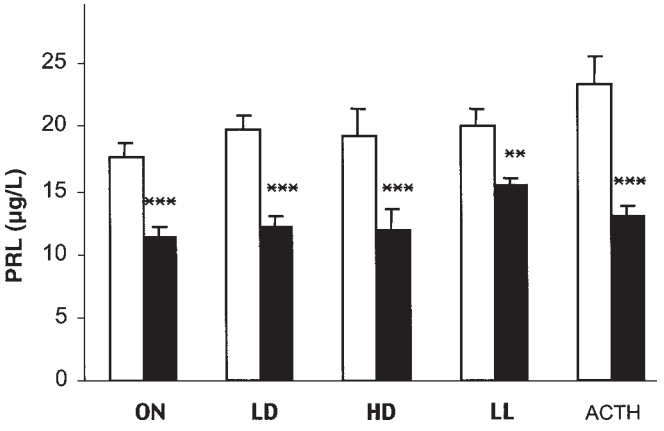

Fig. 1. Serum PRL levels overnight (ON) (1 mg at 12:00 AM; $n = 98$), low-dose (LD) (4 × 0.5 mg for 2 d; $n = 52$), high-dose (HD) (4 × 2.0 mg for 2 d; $n = 29$), and long-lasting (LL) (4 × 0.5 mg for 5 d; $n = 70$) DEX test, and before and after 250 µg of before (□) and after (■) adrenocorticotropin (ACTH) administration ($n = 66$) on same parameters in all patients (mean ± SEM). $^{**}p < 0.01$ and $^{***}p < 0.001$ vs baseline.

basal or in TRH-induced PRL response of nine healthy subjects *(25)*.

The effect of ACTH on PRL secretion has also been analyzed. Following administration of ACTH, plasma PRL levels decreased in healthy men or women and remained unchanged in patients suffering from adrenocortical insufficiency ($n = 6$). Additionally, DEX (2 mg/d for 3 d) resulted in a suppression of basal PRL concentrations in all groups *(26)*.

In spite of these data concerning the effects of glucocorticoids on PRL secretion in humans, the literature is quite ambiguous, and the number of patients included in most of these studies are fairly limited. Therefore, the aims of our present investigations were to collect more information about the sensitivity of PRL secretion to adrenal steroid using different doses; to investigate the effect of DEX treatment in normo- and hyperandrogenic female patients, normo- and hyperprolactinemic patients, and nonobese and obese patients; to analyze the effect of ACTH administration and of the consecutive endogenous cortisol release on plasma PRL levels in a large number of patients.

Results

As expected, all types of DEX treatment significantly decreased cortisol levels (ON: 61.8 ± 8.3 vs 455 ± 17, $n = 97$; LD: 77 ± 11 vs 499 ± 51, $n = 52$; HD: 121 ± 14 vs 556 ± 48, $n = 29$; LL: 36.7 ± 8.2 vs 403 ± 16.4 nmol/L, $n = 71$; $p < 0.001$ for all treatments) (see Materials and Methods for definitions of treatment abbreviations). Injection of ACTH significantly increased (423 ± 47 vs 753 ± 61 nmol/L, $n = 66$; $p < 0.001$) serum cortisol levels. In addition, both DEX and ACTH administration resulted in a significant reduction in serum PRL levels (Fig. 1). The effect of DEX seems to be dose dependent because the most prominent decrease in plasma PRL level could be detected in response to HD DEX in all patients (Table 1). Decreases in serum PRL following DEX treatment were more pronounced in hyperprolactinemic compared with normoprolactinemic patients following the treatments (except in normoprolactinemic patients receiving HD DEX) (Fig. 2). Comparison of cycling and noncycling (postmenopausal + amenorrheic) women revealed a significant difference only in the response of PRL to the ON DEX test. The suppression was more pronounced in the noncycling group (Table 2). There was a positive correlation of basal levels of PRL to changes in serum PRL following all treatment modalities in both normo- and hyperprolactinemic patients (Table 3).

There was no difference between nonobese and obese patients in response of PRL (ΔPRL) to DEX or ACTH (ON DEX test: 5.8 ± 0.7 µg/L, $n = 36$ vs 5.5 ± 0.6 µg/L, $n = 61$; LD DEX test: 7.7 ± 1.0 µg/L, $n = 24$ vs 6.5 ± 0.7 µg/L, $n = 28$; HD DEX test: 6.1 ± 0.9 µg/L, $n = 15$ vs 6.8 ± 0.9 µg/L, $n = 14$; LL DEX test: 2.7 ± 0.3 µg/L, $n = 40$ vs 2.6 ± 0.3 µg/L, $n = 30$; ACTH test: 10.0 ± 1.2 µg/L, $n = 37$ vs 9.8 ± 1.3 µg/L, $n = 29$). There was no difference between female and male patients in PRL response during the tests (ON DEX test: 6.3 ± 0.9 vs 5.5 ± 0.7 µg/L; LD DEX test: 7.8 ± 1.0 vs 7.4 ± 1.0 µg/L; HD DEX test: 7.7 ± 1.2 vs 7.0 ± 0.8 µg/L). Normo- and hyperandrogenic female patients did not differ in PRL response (ON DEX test: 4.4 ± 0.9 µg/L, $n = 18$ vs 5.7 ± 0.7 µg/L, $n = 11$; LD DEX test: 5.4 ± 1.0 µg/L, $n = 11$ vs 7.9 ± 1.0 µg/L, $n = 9$; HD DEX test: 6.3 ± 1.2 µg/L, $n = 9$ vs 4.9 ± 0.8 µg/L, $n = 5$; LL DEX test: 2.2 ± 0.5 µg/L, $n = 31$ vs 3.9 ± 0.7 µg/L, $n = 40$; ACTH test: 7.0 ± 1.1 µg/L, $n = 26$ vs 12.5 ± 1.9 µg/L, $n = 40$, respectively).

Discussion

Our data clearly show that pituitary PRL release can also be influenced by DEX treatment in humans. This synthetic steroid dose dependently reduced plasma PRL in all groups of patients as well as in healthy subjects (Fig. 1). The degree of reduction depended on serum PRL levels and was higher in hyperprolactinemic patients (Fig. 2). Since the hormonal influences on the pituitary are very different in cycling and noncycling (postmenopausal + amenorrheic) women, these subgroups of patients were also compared. A slightly significant difference was found only in the noncycling group during ON DEX test; both the basal levels of PRL and the degree of suppression were higher in these patients (Table 2). Regardless of the DEX test used—except in the HD group—and also in the ACTH test, the normoprolactinemic women had less PRL response than hyperprolactinemic patients (Table 1). Interestingly, this effect of DEX does not require high doses.

The modulation of PRL secretion during physiologic and/or pathologic elevation of glucocorticoid levels may be a result of an alteration at the hypothalamus indirectly, through an increase in the opioid tone *(23,27)*, and directly

Table 1
Decrease in PRL (ΔPRL; μg/L, expressed in % of baseline)
as Response to Different Types of DEX Suppression Test in Normo- and Hyperprolactinemic Patients[a]

	All patients (n = 19)		Patients with Normoprolactinemia (n = 112)		Patients with Hyperprolactinemia (n = 85)	
Treatment[b]	ΔPRL (μg/L)	ΔPRL%	ΔPRL (μg/L)	ΔPRL%	ΔPRL (μg/L)	ΔPRL%
ON	6.4 ± 0.4	32.7 ± 2.2	3.1 ± 0.4[e]	20.0 ± 2.5[e]	11.4 ± 1.2	42.5 ± 3.2
LD	7.7 ± 0.8	36.1 ± 2.9	3.3 ± 0.4[e]	26.9 ± 4.0[f]	10.6 ± 1.3	42.0 ± 4.3
HD	7.6 ± 1.0	39.1 ± 3.7[c]	4.0 ± 0.4[e]	33.9 ± 3.9	10.8 ± 1.5	43.8 ± 6.0
LL	4.7 ± 1.3[h]	7.8 ± 4.7[d]	−1.3 ± 0.7[e]	−13.3 ± 6.4[e]	9 ± 1.3	28.9 ± 3.5
ACTH	10.3 ± 1.4	36.0 ± 2.7	7.0 ± 1.2[g]	30.9 ± 1.8[g]	13.6 ± 1.5	41.0 ± 4.2

[a]Data are the mean ± SE.
[b]ON = overnight (1 mg at 12:00 AM), LD = low-dose (4 × 0.5 mg for 2 d), HD = high-dose (4 × 2.0 mg for 2 d), and LL = long-lasting (4 × 0.5 mg for 5 d) DEX test; ACTH = adrenocorticotropin (250 μg intravenously) test.
[c]$p < 0.001$ vs ON DEX treatment.
[d]$p < 0.001$ vs other treatment.
[e]$p < 0.001$ vs patients with hyperprolactinemia.
[f]$p < 0.01$ vs patients with hyperprolactinemia.
[g]$p < 0.05$ vs patients with hyperprolactinemia.
[h]$p < 0.001$ vs ACTH administration.

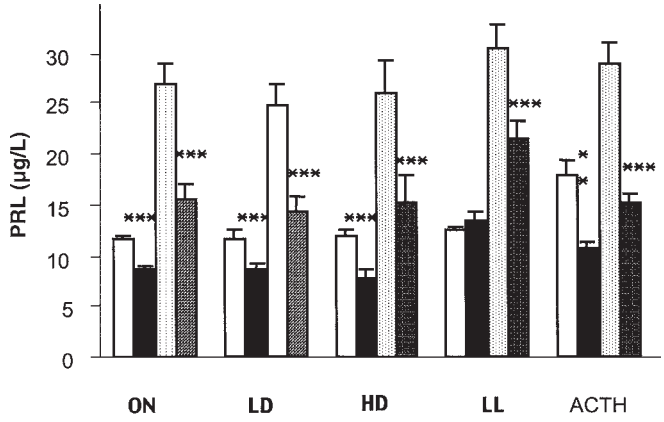

Fig. 2. Serum PRL levels in patients with normoprolactinemia before (□) and after (■) and in patients with hyperprolactinemia before (▥) and after (▨) overnight (ON) (1 mg at 12:00 AM; n = 64 vs 34), low-dose (LD) (4 × 0.5 mg for 2 d; n = 21 vs 34), high-dose (HD) (4 × 2.0 mg for 2 d; n = 16 vs 13), and long-lasting (LL) (4 × 0.5 mg for 5 d; n = 43 vs 27) DEX test, and before and after 250 μg of adrenocorticotropin (ACTH) administration (n = 35 vs 31) (mean ± SEM). **$p < 0.01$ and ***$p < 0.001$ vs baseline.

Table 2
Serum PRL Levels in Cycling and Noncycling (Postmenopausal + Amenorrhoic) Women Before and After Overnight, Low-Dose, High-Dose, and Long-Lasting DEX Test, and Before and After 250 μg of ACTH Administration (n = 21 vs n = 45)[a]

	PRL	ON	LD	HD	LL	ACTH
Cycling women (n = 76)	Before treatment	14.4 ± 1.9	17.9 ± 2.0	17.8 ± 2.0	14.8 ± 1.8	16.1 ± 1.9
	After treatment	9.8 ± 1.5	11.2 ± 1.7	11.2 ± 1.6	14.3 ± 1.7	10.0 ± 1.4
	—	4.6 ± 0.7	6.7 ± 0.9	6.6 ± 0.8	0.5 ± 0.1	6.1 ± 0.8
Postmenopausal+ amenorrheic	Before treatment	19.6 ± 1.8	21.0 ± 1.8	14.9 ± 1.7	21.4 ± 1.6	26.0 ± 2.1
women (n = 93)	After treatment	11.9 ± 0.5	11.7 ± 0.6	11.5 ± 0.4	17.2 ± 1.9	13.8 ± 0.8
	—	7.7 ± 0.7	9.3 ± 0.9	3.4 ± 0.5	4.2 ± 0.6	12.2 ± 0.8
p		0.05	0.32	0.20	0.07	0.12

[a]Decrease in PRL (ΔPRL) is given as mean ± SE. ON = 1 mg at 12:00 AM (n = 43 vs 53); LD = 4 × 0.5 mg for 2 d (n = 19 vs 24); HD = 4 × 2.0 mg for 2 d (n = 8 vs 13); LL = 4 × 0.5 mg for 5 d (n = 27 vs 44).

Table 3
Correlation Between Basal PRL and ΔPRL Values After Each Treatment[a]

	All patients (n = 197)		Normoprolactinemic patients (n = 112)		Hyperprolactinemic patients (n = 85)	
	r	p	r	p	r	p
ON	0.80	<0.001	0.65	<0.001	0.64	<0.001
LD	0.69	<0.001	0.66	<0.001	0.55	<0.01
HD	0.68	<0.001	0.75	<0.001	0.79	<0.01
LL	0.73	<0.001	0.62	<0.001	0.55	<0.05
ACTH	0.96	<0.001	0.97	<0.001	0.92	<0.001

[a] ON = overnight (1 mg at 12:00 AM), LD = low-dose (4 × 0.5 mg for 2 d), HD = high-dose (4 × 2.0 mg for 2 d), and LL = long-lasting (4 × 0.5 mg for 5 d) DEX text; ACTH = adrenocorticotropin (250 μg intravenously) test.

by the multidrug resistance molecule, P-glycoprotein, which is expressed by endothelial cells at the blood-brain barrier *(28)* and is supposed to be responsible for preventing penetration of DEX into the hypothalamus *(29)*. On the other hand, the inhibitory influence of glucocorticoids on PRL secretion might proceed predominantly on the pituitary gland, which is out of the blood-brain barrier, by repressing transcription of the PRL gene *(27,30)*. The potential mediator could be annexin 1 (lipocortin 1), the member of the annexin family of Ca^{2+}- and phospholipid-binding proteins *(31)*. Annexin 1 has been localized in both the hypothalamus and pituitary gland in animals *(32)*. Another possible mediator, the cholinergic neurotransmitter acetylcholine (ACh), is produced in corticotrophs and is acted through a muscarinic receptor *(33–36)*. This conclusion is based on the findings that immunoreactivity for choline acetyl transferase *(37)*, the enzyme catalyzing the biosynthesis of ACh, and cholinesterase activity *(38)* can be predominantly localized in corticotrophs. Moreover, atropine, a potent muscarinic receptor antagonist, dose dependently increases PRL release in reaggregated cells of in vitro culture of the anterior lobe, where paracrine regulatory mechanisms are very similar to the *in situ* pituitary gland *(33)*. The addition of cholinergic agonists to monolayer cultures of anterior lobe cells (where paracrine communications are less abundant) inhibits PRL secretion *(39,40)*. A more recent study has shown that cortisol can inhibit PRL release through a reduction in cellular Ca^{2+} and cyclic adenosine monophosphate levels *(41)*.

Our results show that pituitary mammotrophs are highly sensitive to relatively small changes in the activity of the hypothalamo-pituitary-adrenal (HPA) axis. We can conclude that the HPA system may provide a physiologically important signal to the regulatory mechanisms of PRL secretion. Our finding that a single ACTH injection can reduce plasma PRL in humans supports this view (Figs. 1 and 2). Furthermore, it clearly demonstrates that the increase in the endogenous cortisol level can also inhibit PRL secretion. Thus, we conclude that the pituitary PRL secretion is under a tight feedback control not only from the hypothalamus but also from the HPA system.

Materials and Methods

Subjects

One hundred ninety-seven patients (169 female, 28 male; age: 18–66 yr; median age: 25 yr) with a suspected glucocorticoid overproduction were tested by four different doses of DEX: overnight suppression test ([ON], 1 mg at 12:00 AM), standard low-dose, ([LD],4 × 0.5 mg/d for 2 d, standard high-dose ([HD], 4 × 2 mg/d for 2 d), and long lasting ([LL] 4 × 0.5 mg/d for 5 d). Suspicion of hypercorticolism was raised on the basis of the clinical and radiologic status (i.e., hypertension, obesity, hirsutism, disturbance of menstruation, or accidentally diagnosed pituitary or adrenal adenoma). Sixty-six female patients (age: 18–39 yr, median age: 25 yr) with a suspected ACTH-dependent hyperandrogenism were tested for 17-α-hydroxyprogesterone response to ACTH (Synacthen, 250 μg intravenously; Novartis). In certain patients, different types of treatment were completed. Patients with cortisol excess were excluded from the study. Eighty-five patients (67 female and 18 male; age: 18–66 yr; median age: 26 yr) had hyperprolactinemia and 112 patients (102 female and 10 male; age: 18–66 yr; median age: 27 yr) had normoprolactinemia. One hundred ten patients (97 female and 13 male; age: 18–66 yr; median age: 29 yr; body mass index [BMI] ≥ 27 kg/m^2) were obese and 87 patients (72 female and 15 male; age: 18–63 yr; median age: 25 yr, BMI < 27 kg/m^2) were nonobese. A female patient was considered hyperandrogenic if serum testosterone and/or androstenedione was above the normal range.

Determination of Serum Hormones

Blood samples were collected before treatment and 6 h following the last dose of DEX, or 60 min after ACTH admin-

istration. Levels of serum hormones were measured by specific immunoassay kits for cortisol (Delfia, Wallac) (normal range in the morning: 244–727 nmol/L; sensitivity: 15 nmol/L; intraassay coefficient of variation (CV): 4.5%; interassay CV: 3.5%), PRL (Hungarian Institute of Isotopes) (normal range in female: 5–18 μg/L, in males: 5–15 μg/L; sensitivity: 0.6 μg/L; intraassay CV: 2.0%; interassay CV: 4.7%), testosterone (Delfia, Wallac) (normal range in females: 0.6–3.7 nmol/L; intraassay CV: 5.2%, interassay CV: 8.0%; sensitivity: 0.4 nmol/L), androstenedione (DiaSorin; radioimmunoassay [RIA] (normal range in females: 0.47–2.68 μg/L; intraassay CV: 2.7%; interassay CV: 4.8%; sensitivity: 0.03 μg/L), and 17-α-hydroxyprogesterone (CIS; RIA) (normal range in follicular phase: 0.9–3.9 nmol/L; intraassay CV: 7.5%; interassay CV: 9.9%; sensitivity: 0.06 nmol/L). All investigations were approved by the local ethical committee.

Statistical Analyses

Statistical analyses (Statistica) were performed using the student's paired *t*-test to compare the changes in hormone levels following different treatments, and the unpaired *t*-test to compare different groups. A p value of < 0.05 was considered significant. Regression analysis was also used to detect any association that might exist between the parameters. Results are expressed as the mean ± SEM.

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