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## Dexamethasone Fails to Suppress β-Endorphin Plasma Concentrations in Humans and Rhesus Monkeys

Abstract. *In humans and rhesus monkeys, dexamethasone decreased concentrations of plasma cortisol but did not alter circulating β-endorphin immunoreactivity. Contrary to current theory suggesting that pituitary β-endorphin and adrenocorticotropic hormone are controlled by identical regulatory mechanisms for synthesis and release, our evidence suggests that in higher primates the established glucocorticoid feedback mechanism for the adrenocorticotropic hormone-cortisol system does not regulate β-endorphin secretion in the same way.*

Rats subjected to acute stress by limb fracture or footshock show concurrent increases in plasma adrenocorticotropic hormone (ACTH) and β-endorphin, whereas hypophysectomized rats fail to show this response (*1*). In addition, rats treated with dexamethasone show a concomitant decrease in plasma ACTH and β-endorphin (*1*). These observations are the foundation of a current hypothalamic-pituitary stress hypothesis suggesting that ACTH and β-endorphin are released simultaneously from the pituitary gland and that the regulatory mechanisms (hypothalamic releasing factors and glucocorticoid feedback) involved in the secretion and biosynthesis of both neuropeptides are common and identical.

Tissue culture experiments from normal mouse pituitary gland and a mouse pituitary tumor cell line (AtT-20) also support this hypothesis (*2*). A common polypeptide precursor of ACTH and β-lipotropin (pro-opiocortin) has been identified by using AtT-20 cells known to secrete ACTH, β-lipotropin, and β-endorphin, the last being a fragment of β-lipotropin (amino acid residues 61-91) (*2*). When these cultures are exposed to the synthetic glucocorticoids dexamethasone and prednisolone, the secretion of β-endorphin from these cells decreases in a dose-dependent fashion (*3*).

By using a dose of dexamethasone that markedly reduces plasma cortisol and ACTH in normal humans for up to 24 hours (*4*), we investigated the proposed common regulatory mechanism for the pituitary β-endorphin and ACTH-cortisol systems in humans and rhesus monkeys. One milligram of dexamethasone was given orally to nine adult humans (seven males and two females) who had no medical illnesses and were taking no medications. The single dose was given at 2300 hours as part of the standard overnight dexamethasone suppression test (*5*). After an overnight fast, blood samples were obtained from human subjects at 0800 hours on the mornings before and after dexamethasone was administered. In addition, nine adult male rhesus monkeys in individual cages were given an equivalent dose of dexamethasone, 0.017 mg per kilogram of body weight, intramuscularly, at 2300 hours. On the night before the baseline blood samples were drawn, the monkeys were given saline intramuscularly at 2300 hours as a control procedure (*6*).

The results shown in Fig. 1 indicate that in both humans and monkeys a reduction, averaging 75 percent, in plasma cortisol concentrations occurred 9 hours after dexamethasone administration. In contrast, plasma β-endorphin immunoreactivity remained essentially unaffected by dexamethasone administration in humans and monkeys.

Two differences between our experiment and the previously described rat stress experiment (*1*) in which dexamethasone suppressed both ACTH and β-endorphin may account for the discrepant results. First, the regulatory mechanisms for the synthesis and secretion of β-endorphin in higher primates may differ from those in rodents. Rodents, unlike humans, have a pituitary gland with a functional intermediate lobe thought to be important in the conversion of β-lipotropin to β-endorphin (*7*). Second, in the studies with rats, dexamethasone was administered over a 12-day period in doses more than 100 times greater than those sufficient to suppress stress-mediated increases in corticosterone concentrations in adult rats, and 5000 times greater than those required to suppress the rat corticosterone circadian cycle (*8*). In contrast, in our study, humans and monkeys were given a single low dose of dexamethasone sufficient to suppress ACTH and cortisol secretion.

Although a dissociation between β-endorphin and cortisol release has not been reported previously, dexamethasone given to seven normal human subjects at midnight suppressed plasma ACTH and β-lipotropin to undetectable levels but did not alter the amount of cir-

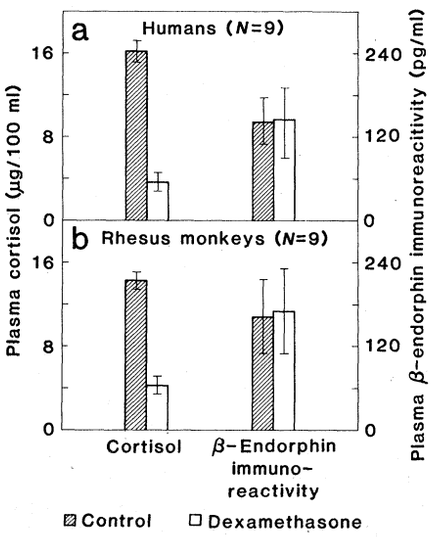


Fig. 1. The mean plasma cortisol concentrations ± standard deviation before and after dexamethasone administration were, respectively, 16.21 ± 4.88 and 3.68 ± 4.63 μg/100 ml in humans and 14.28 ± 4.26 and 4.34 ± 3.5 μg/100 ml in monkeys. In both humans and monkeys the cortisol concentrations after dexamethasone administration were significantly different from those before treatment ($P < .001$, two-tailed paired $t$-test). In the humans the baseline mean β-endorphin immunoreactivity value was 143.2 ± 34.1 pg/ml, and after dexamethasone treatment it was 145.6 ± 55.4 pg/ml; the immunoreactivity of the monkeys increased from a mean value of 163.3 ± 52.7 to 171.4 ± 61.5 pg/ml. Plasma β-endorphin immunoreactivity and cortisol determinations were performed with radioimmunoassay kits (New England Nuclear) with antiserum from rabbits prepared against synthetic human β-endorphin (*13*) and cortisol 21-succinyl bovine albumin, respectively (*14*). The antibody for β-endorphin demonstrates a 50 percent cross-reactivity with β-lipotropin, but less than 0.01 percent with α-endorphin and α-melanocyte stimulating hormone, and less than 0.004 percent with [Leu]enkephalin and [Met]-enkephalin.


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culating opioid pentapeptide, [Met]enkephalin, in one recent investigation (*9*). Plasma β-endorphin concentrations were apparently not measured in that study. Another group reported a similar reduction in β-lipotropin to undetectable levels in three patients treated with dexamethasone (*10*). The suppression of plasma β-lipotropin by dexamethasone (*9, 10*) suggests that, in our study, the β-endorphin antibody with a 50 percent cross-reactivity to β-lipotropin was not measuring β-lipotropin but was probably more specific for β-endorphin in the plasma samples taken after dexamethasone administration.

These findings of suppressed ACTH and β-lipotropin after treatment with dexamethasone and our evidence for the lack of β-endorphin suppression by dexamethasone suggest another pathway for β-endorphin release not directly linked to the ACTH secreting system. Along this line, it has recently been shown with immunohistochemical techniques that β-endorphin immunoreactivity and ACTH are not necessarily present in the same human anterior pituitary cells simultaneously (*11*). In addition to its location in the pituitary gland, β-endorphin has been found in other parts of the brain and in peripheral organs such as the pancreas (*12*), although no direct evidence is available yet to indicate that ACTH-independent pituitary cells or tissues of the brain or of peripheral organs contribute to the production of plasma β-endorphin. Our data indicate a dissociation between the effects of a low dose of dexamethasone on plasma β-endorphin and plasma cortisol concentrations. We conclude that in humans and rhesus monkeys the feedback mechanisms regulating the hypothalamic-pituitary-adrenal system and the β-endorphin system are not identical.

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## Phase-Sensitive Midbrain Neurons in *Eigenmannia*: Neural Correlates of the Jamming Avoidance Response

Abstract. *Neurons in the torus semicircularis of the weakly electric fish* Eigenmannia *encode phase differences between sinusoidal electrical stimuli received in different body regions. These fish normally experience time-varying phase differences when the electric organ discharge fields of two or more individuals overlap. These phase differences supply information necessary for the animal's jamming avoidance behavior.*

South American weakly electric fish [gymnotoid fish (*1*)] generate electric fields by rhythmically discharging electric organs located in their elongate tails. This field results in a voltage generated across the skin (transepidermal voltage), which is monitored by electroreceptors distributed over the animal's surface. Objects having an electrical impedance different from that of the surrounding water distort this electric field, thereby altering the transepidermal voltage patterns associated with the electric organ discharge (EOD). The animals can "electrolocate"—detect and identify objects in their environment—by analyzing the patterns of transepidermal voltage encoded by their electroreceptors (*1a*).

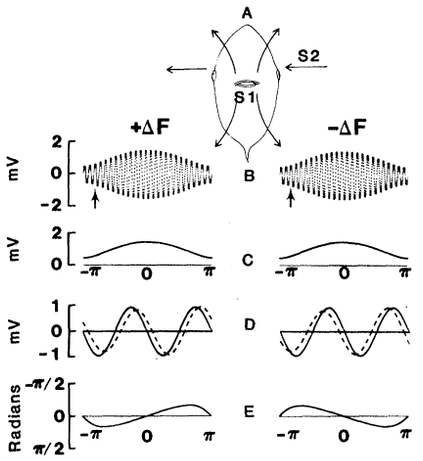


Fig. 1. (A) Head-on view of *Eigenmannia* illustrating the patterns of current flow resulting from the radially presented EOD replacement, *S1*, and the transversely presented jamming signal, *S2*. (B) Beat waveform produced by the addition of *S1* and *S2*; $\Delta F$ = 4 Hz. The *S1* frequency was set at 100 Hz for illustrative purposes. (C) Envelopes of the signals of (B). These are identical for opposite $\Delta F$'s as long as the two components of the beat, *S1* and *S2*, are sinusoidal. (D) Individual cycles of the beat waveform (dashed lines) from the region indicated by the arrows in (B) on an expanded time scale. The solid lines show the *S1* component of these waveforms. The phase relationships between these two signals are opposite for the two signs of $\Delta F$. (E) Plots of the phase of the beat waveform relative to the *S1* over the time of one beat cycle. The depths of the amplitude modulation (C) and of the phase modulation (D) approach zero as the intensity of *S2* approaches zero.

An individual's electrosensory system is sensitive to electrical signals of any origin as long as those signals meet the amplitude and frequency requirements of the electroreceptors (*2*). Therefore, certain extraneous signal sources can interfere with the animal's analysis of its personal electric field; that is, the system is sensitive to jamming (*3*). Extraneous signals similar in amplitude and frequency to the animal's own EOD significantly impair electrolocation (*4*). Conspecifics, of course, form a large population of sources of jamming signals in the animal's environment, and the fish have evolved a jamming avoidance response (JAR) that reduces the deleterious effects of jamming signals (*3-5*).

We studied the gymnotoid fish *Eigenmannia virescens*, which has nearly sinusoidal EOD's of stable, though individually different, fundamental frequency (*F1*) between 250 and 600 Hz. Electrolocation is most severely impaired if the animal is exposed to a second EOD-like signal having a slightly different frequency (*F2*). Signals separated by difference frequencies ($\Delta F$, where $\Delta F = F2 - F1$) ranging between ± 2 to ± 8 Hz are most detrimental; fish ex-


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