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Effects of Naloxone upon Prolactin and Cortisol in Normal Women (40878)

J. BLANKSTEIN,[1] F. I. REYES, J. S. D. WINTER, AND C. FAIMAN[2]

Departments of Obstetrics and Gynaecology, Physiology, Paediatrics and Medicine, University of Manitoba, and the Endocrine-Metabolism Laboratory Health Sciences Centre, Winnipeg, Manitoba, Canada

Abstract. In order to assess whether endogenous opioids are involved in the regulation of prolactin and ACTH, we examined the effects of iv administration of naloxone (10 mg) to 10 normal women. In 6 of these subjects, a saline control study (randomized design) was also performed. There was no change in serum prolactin following naloxone or saline. In contrast, naloxone resulted in an increment in serum cortisol from a mean of 8.7 μg/dl prior to treatment to a peak of 12.7 μg/dl at 60 min. Values between 45 and 75 min were significantly higher than those following saline injection. The increment of cortisol following naloxone administration suggests the presence of an inhibitory opioid influence upon basal ACTH secretion in man.

Opiates and enkephalin analogues have been shown to stimulate prolactin secretion in the rat (1–3), nonhuman primate (4), and in man (5–7). The finding that specific opiate antagonists not only block this effect of administered opioids (1, 2, 4) but also result in a reduction of prolactin levels in untreated animals (4, 8) has led to the conclusion that endogenous opioids may be normally involved in prolactin regulation. This hypothesis has not been tested rigorously in man and preliminary reports are conflicting (9–13).

The effect of opioids on ACTH regulation in man also has received scant attention. Narcotic drugs as well as enkephalin analogues appear to reduce circulating ACTH and cortisol levels (6, 14, 15). Preliminary reports indicate that naloxone, a selective opiate antagonist, results in stimulation of the hypothalamo–pituitary adrenal axis (9, 11, 16), suggesting that ACTH secretion is under tonic inhibition by an opioid pathway in man.

The purpose of the present study was to explore further the hypothesis that endogenous opioids are involved in the physiologic regulation of prolactin and ACTH secretion by assessing the effects of naloxone on circulating levels of prolactin and cortisol in normal women.

Materials and methods. Ten healthy women ranging in age from 20 to 34 years volunteered for this study. All had regular menses and were studied during the follicular phase of the cycle. Subjects reported to the laboratory at 0800 hr and rested for 1 hr. A slow intravenous infusion was then started, through which samples of blood were withdrawn every 15 min. At the beginning of the second hour, 10 mg naloxone (Endo Laboratories, Garden City, N.Y.) in 1 ml saline were injected as an iv bolus. Blood pressure and pulse rate were measured every 10 min throughout the study. In six of the women, a control study was performed during the follicular phase of the preceding or the next menstrual cycle using the same protocol with infusion of 1 ml saline. The order of treatment was randomized and infusions were done in single-blind fashion.

Measurements of serum prolactin and cortisol were performed by previously described radioimmunoassay techniques (17, 18). Blood glucose levels were determined by the glucose oxidase autoanalyzer method. The significance of differences in hormone concentrations between the naloxone- and saline-infused groups, and of pre- versus posttreatment mean levels was assessed by analysis of variance using a

[1] Present address: Department of Obstetrics and Gynaecology, Tel Hashomer Hospital, Israel.

[2] Reprint requests: Dr. C. Faiman, G449-Health Sciences Centre, 700 William Ave., Winnipeg, Manitoba, R3E 0Z3 Canada.

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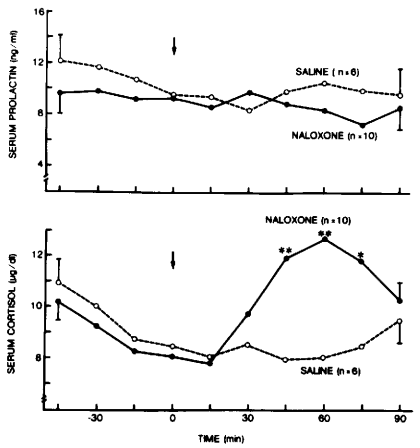

FIG. 1. Mean serum prolactin and cortisol responses to naloxone (10 mg i.v.) and saline injection at time 0, indicated by arrows. Asterisks indicate significant differences between mean values of both groups at corresponding times (**$P < 0.01$; *$P < 0.05$). The overall standard errors for each group are plotted at both ends of the figure.

mixed factorial design program (19) and Duncan's multiple range test (20).[3]

Results. The serum prolactin and cortisol responses to naloxone are shown in Fig. 1. Prolactin levels did not change following either naloxone or saline administration. There were no significant differences between mean levels of the two groups at all time periods. Pretreatment cortisol levels were similar in both groups. Naloxone injection resulted in an increase in mean cortisol levels from 8.7 µg/dl prior to treatment to a peak of 12.7 µg/dl at 60 min ($P < 0.01$). Cortisol values from 45 to 75 min inclusive were significantly higher in the naloxone-treated group than in the control group.

No change in blood glucose level, blood pressure, and pulse rate was observed in either group throughout the study.

[3] This analysis of variance was designed so as to recognize that the effects of the two treatments were derived from two groups of subjects while the time effect was measured across subjects. In addition, a factorial analysis of variance in randomized complete blocks was performed utilizing data solely from the six subjects who had undergone both treatments. The results were both qualitatively and quantitatively similar to those from the first analysis and accordingly are not shown.

Discussion. Opioid administration elicits a significant increment in serum prolactin levels in man (5–7). Naloxone, an opiate antagonist possessing virtually no agonistic properties (21), not only attenuates this effect on prolactin in man (6) but can also cause a reduction in basal prolactin levels in the rat (2) and non-human primate (4). These observations suggest that endorphins may be involved in the regulation of prolactin secretion in these latter species. Our failure to observe a naloxone-induced decline in prolactin levels in the present study is in keeping with most (9, 10, 12, 22), but not all (13), findings in human subjects and suggests that opioid pathways are not involved in basal prolactin secretion in man during the waking hours. Furthermore, the nocturnal (late sleep) rise of serum prolactin was not observed to be influenced by infusions of lower doses (0.8 mg/hr) of naloxone in a recent study of five women (23).

In contrast, naloxone did elicit a significant increment in serum cortisol levels (Fig. 1), a finding in agreement with two preliminary reports in man (11, 16). A direct effect of the drug on the adrenal gland has not been ruled out but seems unlikely since opiates themselves do not influence adrenal responses to ACTH (14). Furthermore, the rise in serum cortisol appears to be preceded by an elevation of plasma ACTH levels (16). It is unlikely that these ACTH–cortisol increments are due to a nonspecific stress response to the high dose of naloxone administered (25 times the usual adult dose of 0.4 mg used in treating narcotic overdoses) since no effects on the cardiovascular system were observed, blood glucose levels remained unchanged, and the subjects experienced no untoward symptoms following the naloxone injection. Taken together, these observations suggest that an inhibitory opioid pathway is involved in the basal regulation of ACTH and that this inhibition is unmasked by naloxone. Since the predominant neural regulation of ACTH secretion in man appears to involve a stimulatory serotoninergic pathway (24), it is tempting to speculate that an opioid–serotonin interaction (25) may underlie the observed effects of naloxone. However, the

above study (25) suggests that the opioid pathway involving serotonin release is stimulatory in nature, whereas we would have to postulate the unmasking of an inhibitory opioid pathway to explain the naloxone results. Thus, whether the putative opioid pathway modulating ACTH secretion involves serotonin or some other neurotransmitter, or is a direct effect on the pituitary gland, itself, remains to be elucidated.

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