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# Effect of morphine on the hypothalamic-pituitary axis in postmenopausal women

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*In this study, 10 postmenopausal women were given 5 mg of morphine intravenously; and the serum level of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH) were measured before and after morphine injection. A significant increase in serum prolactin as well as a significant decrease in LH were observed following the administration of morphine. It is suggested that morphine may affect a common neurotransmitter that controls both prolactin and LH secretion. It is also of interest that the increase in serum prolactin following morphine injection is of similar magnitude as observed in premenopausal patients. Fertil Steril 37:389, 1982*

Opiate receptor activation by exogenous opiates or endogenously occurring ones can affect pituitary function in the experimental animal.[1-4] In man, acute administration of morphine, methadone, or D-alanine-metenkephaline amide results in an increase in serum prolactin (PRL) and occasionally growth hormone (GH).[3-7] The effects are mediated presumably via an alteration of the dopamine release mechanism in the hypothalamus.[8-11] Acute administration of dopamine receptor agonists such as apomorphine or bromocriptine can suppress the stimulating effect upon PRL secretion.[12, 13] In addition, pretreatment with opiate receptor antagonists such as naloxone or naltroxon can block the effect of morphine or methadone upon PRL secretion, suggesting that the effects of morphine are specific for the opiate receptors.[14-16]

It has been shown that PRL secretions can be affected by the levels of endogenous estrogens. In postmenopausal women, a decrease in PRL response occurs to the usual provocation stimuli; and in men treated with estrogens, a sensitization of the pituitary PRL secretion cell can be demonstrated.[17-20]

In order to assess whether acute morphine administration can induce PRL release in hypoestrogenic postmenopausal women, we administered morphine to such women and measured the PRL, GH, and gonadotropin output. The reason we measured serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) was to assess whether acute administration of opiate receptor agonists could suppress the gonadotropin output as described in earlier experiments in monkeys.[1]

## MATERIALS AND METHODS

Ten unpremedicated postmenopausal women who were scheduled for minor gynecologic surgery were the subjects. The experiment was performed prior to surgery. The average age of the patients was 60 years of age. Four 10-ml aliquots of venous blood were obtained at 15-minute inter-

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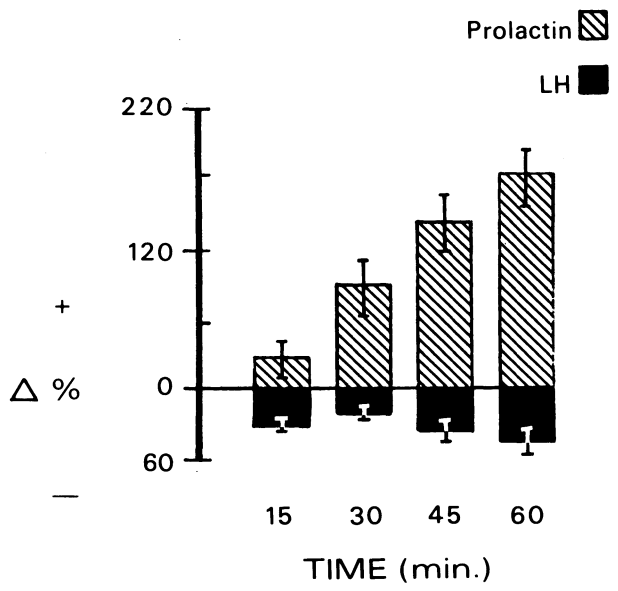


**Figure 1**
Percentage of variation of serum PRL and serum LH from control level (time = 0) to 60 minutes following the intravenous injection of morphine sulfate.

vals from each patient. These served as control samples. Following an intravenous bolus injection of 5 mg morphine sulfate, four more 10-ml blood samples were obtained at 15-minute intervals.

The following determinations were done in each blood sample by radioimmunoassay: LH, FSH, PRL, and GH. The paired Student's *t*-test was used with the mean of the summation of all samples taken prior to the administration of morphine and the means of the experimental periods for each parameter measured.

## RESULTS

Basal serum prolactin and growth hormone levels were within normal range in all women studied (PRL, 14.7 ± 1.21 ng/ml; GH, 1.5 ± 0.2 ng/ml [mean ± standard error]). Serum FSH and LH values were within menopausal range (FSH, 198.5 ± 46.7 μg/dl; and LH, 30.5 ± 6.4 μg/dl [mean ± standard error]) using LER-907 as a standard (Fig. 1). The administration of morphine led to a significant increase in serum PRL ($P < 0.05$) and a decrease in serum LH ($P < 0.05$).

In contrast to the changes occurring in serum PRL and LH values, no significant effects ($P > 0.2$) were noticed on serum GH or FSH, although a general downward trend in FSH level was observed. A typical time-related response pattern of all four hormones after the intravenous administration of morphine can be seen in Figure 2.

## DISCUSSION

These data extend earlier observations showing that in premenopausal women, the administration of morphine induced a rise in serum PRL. In addition, we show that at this dose the quantitative release of PRL is of similar magnitude in postmenopausal women as in premenopausal women.[21] Our failure to show a rise in GH also confirms earlier observations in man in whom morphine or methadone were incapable of inducing a consistent increase in GH. This is opposite to the results reported in rodents.[2, 6]

The mechanisms whereby opiates lead to an increase in PRL are unknown. It is possible that their action is mediated via an alteration of dopamine availability (acting as a neurotransmitter) at the anterior pituitary lactotroph sites. It has been documented that there is a decrease in dopamine turnover in animals treated with exogenous/endogenous opiates.[10, 11]

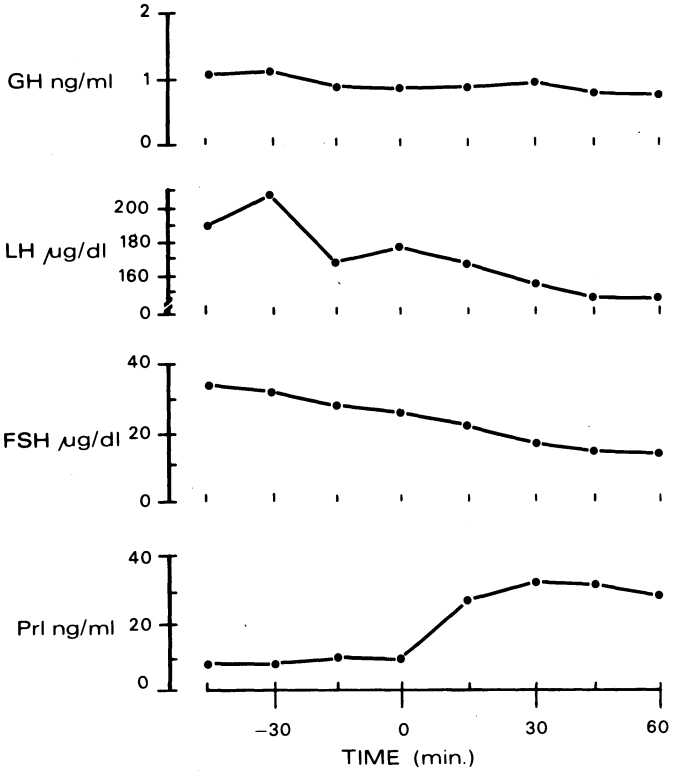


**Figure 2**
Serum GH, LH, FSH, and PRL changes preceding (time −45 minutes to 0) and following (time 0 to 60 minutes) intravenous injection of morphine sulfate in a typical patient.

Our observation of a decrease of serum LH following the administration of morphine is in support of the previous reports showing that the administration of an opiate receptor agonist can suppress circulating gonadotropic concentration in castrated primates.[1, 2]

Finally, the recently described suppressive effect of enkephalin upon LH and PRL in men[4-20, 22] suggests that the endogenous opiates can possibly affect a common neurotransmitter that is involved in the control of both PRL and LH. A most likely candidate is dopamine. It is probable that morphine changes the dopamine turnover in the hypothalamus with a consequent increase in serum PRL and a decrease in serum LH. The hypothesis might be further supported by additional studies showing that morphine suppresses LH secretion in humans and that the administration of LH-releasing hormone (LH-RH) restores LH serum concentrations to normal.

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