

INDOMETHACIN SUPPRESSES PROLACTIN RELEASE IN MEN

Haruo ITO, Kenji KAWAMURA, Zengo KATAUMI, Hidenori SUMIYA,
Masanobu TAKAHARA, Hideo AIKAWA and Jun SHIMAZAKI

From the Department of Urology, School of Medicine, Chiba University, Chiba

Indomethacin administered intrarectally at a dose of 100 mg elicited a statistically significant decrease of serum prolactin level in men. Serum LH level was depressed slightly but the decrease was not statistically significant. There was no effect on serum FSH concentration.

Key words: Prolactin, Indomethacin, Prostaglandin, Gonadotropin

INTRODUCTION

It has been reported that various prostaglandins influence the release of gonadotropins and prolactin^{1,2)}. Controversial results, however, were occasionally demonstrated. Prostaglandin effects should be interpreted carefully because in some instances the results obtained were mediated by changes in the adrenergic system³⁾. The present experiment was undertaken to elucidate the physiological role of prostaglandins in regulating gonadotropin and prolactin release in men by administering indomethacin, a cyclo-oxygenase inhibitor, and measuring the concentrations of serum LH, FSH and prolactin.

MATERIALS AND METHODS

Male volunteers were subjected to the study. They were from 18 to 46 years old, the average age being 33 years old. They had no endocrinological or metabolic disorders. In the early morning, the blood was drawn from antecubital vein for the determination of the basal level. Then, two suppositories of 50 mg indomethacin were put in to their rectums. Blood samples were taken 30, 60, 90 and 120 minutes after the deposition of indomethacin into rectum. Serum LH, FSH and prolactin were measured by radioimmunoassay (double antibody method). Statistical significance was judged by Student's

t test.

RESULTS

The concentrations of serum prolactin before and 30, 60, 90, 120 minutes after indomethacin administration in 8 men were 9.2 ± 1.7 , 9.2 ± 1.8 , 7.6 ± 1.4 , 6.8 ± 1.7 and 6.1 ± 2.1 ng/ml (mean $\pm$ S.D.), respectively (Fig. 1). Thus, the level of prolactin decreased progressively. Statistically significant differences were observed 60, 90, and 120 minutes after the administration of indomethacin.

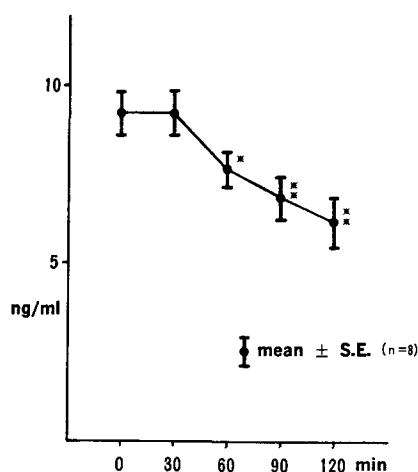


Fig. 1. Effect of indomethacin on serum prolactin level
Significantly different from baseline level.....* $P < 0.05$,
** $P < 0.01$

The concentrations of serum LH before and 30, 60, 90 and 120 minutes after indomethacin administration in 8 men were 17.6 ± 6.6 , 17.5 ± 8.9 , 16.3 ± 6.8 , 14.3 ± 4.3 and 14.5 ± 5.1 mIU/ml (mean $\pm$ S.D.), respectively (Fig. 2). There was a slight decrease in LH levels 90 and 120 minutes after indomethacin administration. However, the difference was not statistically significant.

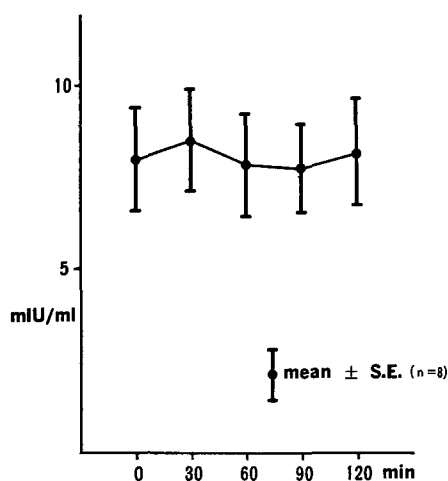


Fig. 2. Effect of indomethacin on serum LH level

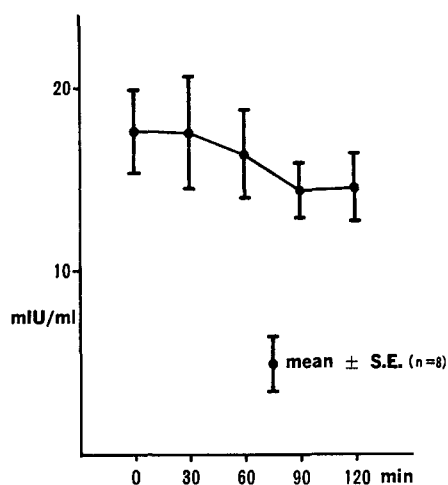


Fig. 3. Effect of indomethacin on serum FSH level

The concentrations of serum FSH before and 30, 60, 90 and 120 minutes after indomethacin administration in 8 men

were 8.0 ± 3.9 , 8.5 ± 4.0 , 7.8 ± 3.9 , 7.7 ± 3.4 and 8.1 ± 3.9 mIU/ml (mean $\pm$ S.D.), respectively (Fig. 3). No change of FSH level was observed by the administration of indomethacin.

DISCUSSION

The present study is the first demonstration that indomethacin, a cyclo-oxygenase inhibitor, suppresses prolactin release. Although the mechanism of the decrease of prolactin release elicited by indomethacin cannot be elucidated from the present observation, the inhibition of prostaglandin production may be the cause of the suppression of prolactin release. It was reported that prostaglandin I_2 infusion caused a dose-dependent increase in plasma prolactin concentrations in men⁴⁾. The stimulation of prolactin release induced by prostaglandin I_2 administration was also shown in rats, although a pharmacological dose was given¹⁾. Furthermore, it was shown that prostaglandin E_1 had a physiological role in stimulating prolactin release at the hypothalamus⁵⁾. Indomethacin inhibited the increase of prolactin level induced by estradiol in ovariectomized rats. This effect was cancelled by the concomitant administration of prostaglandin E_1 or prostaglandin E_2 ⁶⁾. The prolactin suppression cannot be explained by the lowered noradrenalin level caused by indomethacin through the inhibition of prostaglandin production. Prostaglandin E_2 infusion increased plasma noradrenalin concentration in men³⁾, and noradrenalin as well as dopamine depressed prolactin release⁷⁾.

Although many drugs and conditions are known to stimulate prolactin release, prolactin release can be inhibited only by a few agents such as bromocriptine and L-DOPA. Therefore, the fact that indomethacin lowers plasma prolactin level is very interesting. Ferrari et al. reported that the stimulation of pituitary dopamine receptors induced a normal prolactin suppression in hypothalamic hyperprolactinemia patients, whereas central nervous system-acting dopaminergic drugs failed to lower prolactin levels⁸⁾. It will be of

value to investigate the effect of indomethacin on prolactin release in hypothalamic hyperprolactinemia patients to determine the site of action of indomethacin.

It was clearly demonstrated that prostaglandin E_2 caused a dose-dependent release of LH-RH from rat hypothalamic synaptosomes⁹. Furthermore, indomethacin and aspirin inhibited LH-RH release from rat hypothalamic synaptosomes *in vivo* and *in vitro*⁹. Prostaglandin E_2 also elicited an increase of circulating LH in rats¹⁰. In humans prostaglandin $F_{2\alpha}$ did not increase plasma LH and FSH levels¹¹. Indomethacin did not modify LH release in response to an injection of LH-RH¹². Furthermore, the administration of a large dose of aspirin failed to prevent the occurrence of the ovulatory LH peak during the middle part of the menstrual cycle¹³. Our finding that indomethacin did not affect gonadotropin release is in agreement with these previous reports. It may be that the changes in the central control of gonadotropin secretion is too small to be detected by the serum levels of LH and FSH. It is remarkable that indomethacin lowered the prolactin level considering the fact that cyclooxygenase inhibitors do not induce detectable changes in gonadotropins in humans as shown in the present experiment as well as in the above mentioned reports¹¹⁻¹³.

REFERENCES

- 1) Kimball FA, Porteus SE, Kirton KT, Frielink RD, Creasy DM and Dayan AD: Prostacyclin (PGI_2) effects on anterior pituitary hormones in the rat *in vivo*. *Prostaglandins* 18: 377~385, 1979
- 2) Ojeda SR, Wheaton JE and McCann SM: Prostaglandin E_2 -induced release of luteinizing hormone-releasing factor (LRF). *Neuroendocrinology* 17: 283~287, 1975
- 3) Newman WP and Brodows RG: Metabolic effects of prostaglandin E_2 infusion in man: Possible adrenergic mediation. *J Clin Endocrinol Metab* 55: 496~501, 1982
- 4) Patrono C and Canete-Soler R: Recent progress in andrology. In: *Oligozoospermia* Frajese G, Hafez ESE, Conti C and Fabbrini A eds. pp. 167~175, Raven Press, New York, 1981
- 5) Ojeda SR, Naor Z and Negro-Vilar A: The role of prostaglandins in the control of gonadotropin and prolactin secretion. *Prostaglandin Med* 5: 249~275, 1979
- 6) Ojeda SR, Jameson HE and McCann SM: Effects of indomethacin and prostaglandin injections on plasma prolactin and growth hormone levels in rats. *Endocrinology* 102: 531~539, 1978
- 7) Takahara J, Arimura A and Schally AV: Suppression of prolactin release by a purified porcine PIE preparation and catecholamines infused into a rat hypophyseal portal vessel. *Endocrinology* 95: 462~465, 1974
- 8) Ferrari C, Rampini P, Benco R, Caldara R, Scarduelli C and Crosignani G: Functional characterization of hypothalamic hyperprolactinemia. *J Clin Endocrinol Metab* 55: 897~901, 1982
- 9) Soler RC, Casa SD, Pugliese F, Ciabattini G and Patrono C: Evidence for a physiologic role of prostaglandin E_2 in the release of gonadotropin-releasing hormone from rat hypothalamic synaptosomes. *Prostaglandins* 13: 1017, 1977
- 10) Chobsieng P, Naor Z, Koch Y, Zor U and Lindner HR: Stimulatory effect of prostaglandin E_2 on LH release in the rat: Evidence of hypothalamic site of action. *Neuroendocrinology* 17: 12~17, 1975
- 11) Craig GH: The effect of intravenous prostaglandin $F_{2\alpha}$ on serum luteinizing hormone, follicle-stimulating hormone and plasma cortisol in normal men. *J Clin Endocrinol Metab* 41: 180~182, 1975
- 12) Patrono C and Serra GB: Do pituitary prostaglandins play an essential role in the action of LH-RH in man? *Prostaglandins* 6: 345~348, 1974
- 13) Greenway FL and Swerdloff RS: The effect of aspirin (prostaglandin synthetase inhibitor) on ovulation. *Fertil Steril* 30: 364~365, 1978

(Accepted for publication, August 2, 1983)

和文抄録

インドメサシンのプロラクチン放出抑制効果

千葉大学医学部泌尿器科学教室（主任：島崎淳教授）

伊 藤 晴 夫・川 村 健 二・片 海 善 吾
角 谷 秀 典・高 原 正 信・相 川 英 男
島 崎 淳

インドメサシン 100 mg の直腸内投与により男子
血中プロラクチン濃度は推計学的に有意な低下を示し

た。血中 LH レベルは軽度低下したが、有意差はな
かった。血中 FSH は変化しなかった。