Contribution of the Reproductive Hormones to the Regulation of Prostaglandin $F_{2\alpha}$ Production by Immunocompetent Cells

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The ability of estradiol, progesterone, and chorionic gonadotropin to influence prostaglandin $F_{2\alpha}$ production by intact splenocytes of CBA mice was studied. Estradiol and progesterone similarly activated the processes of prostaglandin $F_{2\alpha}$ production. No relationship was revealed between the effect and the concentration of the hormones. Chorionic gonadotropin activated prostaglandin production by immunocompetent cells but only when used in a concentration reflecting the peak of its physiological secretion. Combining gonadotropin with estradiol or progesterone did not lead to any appreciable differences in the prostaglandin-stimulating action of each hormone alone.

Key Words: *prostaglandin $F_{2\alpha}$; chorionic gonadotropin; estradiol; progesterone; splenocytes*

From the immunological viewpoint, pregnancy is still an enigma: a semiallogenic fetus, despite the functional intactness of the maternal lymphocytes, is not subject to immune aggression. Such reproductive hormones as chorionic gonadotropin (CG), estradiol, and progesterone, whose concentrations during pregnancy increase by several orders of magnitude, are known to exert strong immunomodulating effects [2,5,6]. It is possible that these very hormones create the basic prerequisites for normal development of the foreign fetus during gestation. However, the mechanisms of hormonal regulation of immunocompetent cell functioning are not yet quite clear, nor are the results of their combined action.

Prostaglandins (PG) are potent mediators of immunocompetent cells, and therefore the level of their production gives an idea of the functional activity of the immune system cells. The majority of studies of PG have been devoted mainly to PG class E_2 as being the most active immunosuppressive molecules [7]. On the other hand, very few data are available about $PGF_{2\alpha}$, which in a number of cases has an opposite action [1], except for the fact that

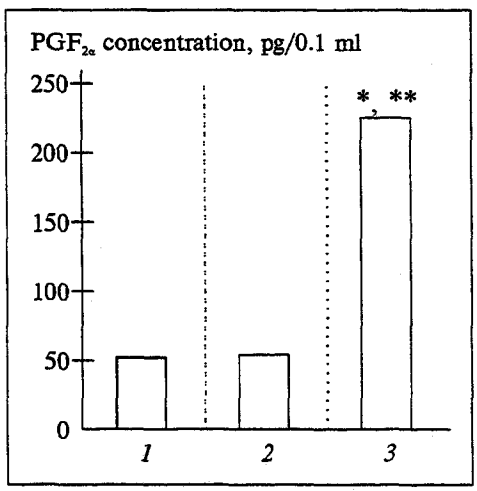

Fig. 1. Level of $PGF_{2\alpha}$ in splenocyte supernatants following one-hour exposure to CG. *1*) control (hormone solvent – medium 199); *2*) CG (10 IU/ml); *3*) CG (50 IU/ml). One asterisk shows $p<0.05$ *vs.* the control, two asterisks *vs.* CG in a concentration of 10 IU/ml.

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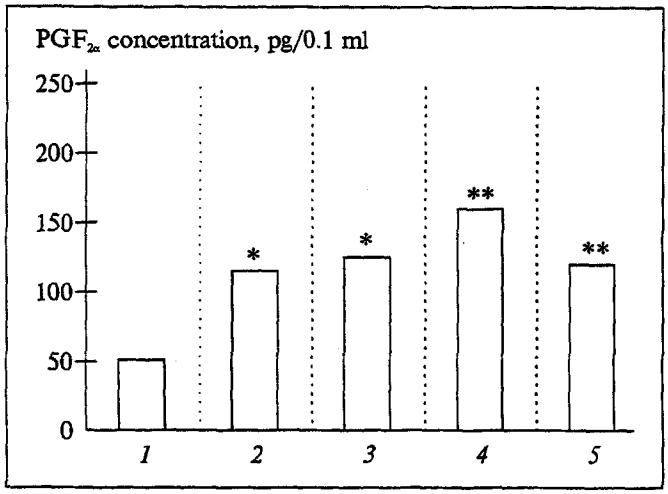

Fig. 2. Level of $PGF_{2\alpha}$ in splenocyte supernatants after one-hour exposure to estradiol and progesterone. *1*) control (hormone solvent – 0.25% ethanol); *2*) estradiol (1 ng/ml); *3*) estradiol (10 ng/ml); *4*) progesterone (20 ng/ml); *5*) progesterone (100 ng/ml). Here and in Fig. 3: one asterisk shows $p<0.001$, two asterisks $p<0.01$, and three asterisks $p<0.05$ *vs.* the control.

its level is closely related to the T-lymphocyte count [8]. Because of the abortive effect of $PGF_{2\alpha}$ and its participation in the regulation of ovulation [4], it is important to study its hormone-mediated production by immunocompetent cells in order to understand the mechanisms of the hormonal control of immune reactions during gestation.

This research was aimed at investigating the abilities of CG, estradiol, and progesterone, in concentrations corresponding to the levels of these hormones during the different trimesters of pregnancy, to influence, individually and together, the production of $PGF_{2\alpha}$ by splenocytes of intact female mice.

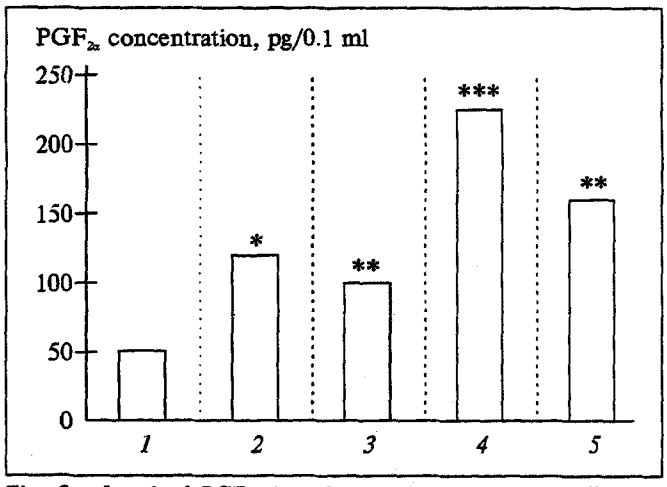

Fig. 3. Level of $PGF_{2\alpha}$ in splenocyte supernatants following one-hour exposure to hormone combinations CG+estradiol and CG+progesterone. *1*) control (hormone solvent); *2*) CG (50 IU/ml)+estradiol (1 ng/ml); *3*) CG (10 IU/ml)+estradiol (10 ng/ml); *4*) CG (50 IU/ml)+progesterone (20 ng/ml); *5*) CG (10 IU/ml)+progesterone (100 ng/ml).

MATERIALS AND METHODS

Adult female CBA mice were used in the experiments. After sacrifice, the spleens were removed under aseptic conditions, and homogenized, and the cells were washed three times in cold medium 199. A splenocyte suspension (5×10^6/ml) was prepared, to which CG (Profasi) was added in doses of 10 or 50 IU/ml, this reflecting the hormone level during trimesters II-III and I, respectively [9]. Estradiol or progesterone (Serva) was used in concentrations of 1-10 or 20-100 ng/ml, respectively. The concentrations of sex steroids correspond to their levels during the trimesters I and III in human pregnancy [4]. In addition, the sex steroids were added in combination with CG in concentrations typical of trimesters I and III.

Splenocytes incubated with hormone solvents formed the control. After the addition of hormones, the splenocyte cultures were incubated for 1 h at 37°C. Then 0.1 ml of culture medium 199 was taken from the supernatant for radioimmunoassay of $PGF_{2\alpha}$ using a standard radioactive kit for measurements of $PGF_{2\alpha}$ (Institute of Isotopes, Hungary). The results were statistically processed using Student's *t* test.

RESULTS

CG in a concentration typical of trimester I (50 IU/ml) reliably stimulated the production of $PGF_{2\alpha}$ by female mouse splenocytes, but when the hormone concentration was reduced to 10 IU/ml, reflecting the CG level during the subsequent trimesters, the stimulating effect completely disappeared (Fig. 1).

Estradiol activated $PGF_{2\alpha}$ production, regardless of the dose. Progesterone in concentrations corresponding to its levels during trimesters I-III reliably stimulated $PGF_{2\alpha}$ secretion by immunocompetent splenocytes. No statistically reliable difference was detected between the concentrations 20 and 100 ng/ml (Fig. 2).

Since the direction of CG immunomodulating effects depends in a number of cases on the ovarian hormones [5], it is necessary to find out how CG combinations with sex steroid hormones can affect the production of $PGF_{2\alpha}$ by splenocytes. Only two types of such combinations were tested: CG+estradiol and CG+progesterone. The concentrations of hormones were selected so that they corresponded to trimester I or III.

Figure 3 shows that none of the studied sex steroids is antagonistic vis-a-vis CG, and vice versa.

Hence, the reproductive hormones may be said to boost the production of $PGF_{2\alpha}$ by immunocompetent cells throughout pregnancy. In contrast to PGE_2, this type of PG activates lymphocyte function [1], which is evidently why injections of CG to intact female mice increase the production of antibody-producing cells [3,5,6]. Voltaren, an inhibitor of PG synthesis, has been shown to suppress the formation of the adoptive immune response, whereas CG and estradiol cancel out this depression [5]. These data permit us to postulate that CG and sex steroids are capable of modulating the immunocompetent cells by activation of $PGF_{2\alpha}$ production and thus trigger mechanisms alternative to immunodepression during gestation.

REFERENCES

1. N. Yu. Gromykhina and V. A. Kozlov, *Immunologiya*, № 5, 11-15 (1982).
2. Yu. I. Shilov and N. N. Kevorkov, *Ibid.*, № 6, 38-41 (1980).
3. S. V. Shirshev, N. N. Kevorkov, and N. I. Sharyi, *Byull. Eksp. Biol. Med.*, **104**, № 9, 337-340 (1987).
4. N. G. Kase and J. V. Reyniak, *Mt. Sinai J. Med. (New York)*, **52**, № 1, 11-34 (1985).
5. N. N. Kevorkov, Ju. I. Shilov, and S. V. Shirshev, *Brain Behav. Immun.*, **5**, 149-161 (1991).
6. N. N. Kevorkov and S. V. Shirshev, *Neurosci. Behav. Physiol.*, **17**, № 5, 448-451 (1987).
7. C. Vercammen and J. L. Ceuppens, *Cell. Immunol.*, **104**, № 1, 24-36 (1987).
8. D. R. Webb and P. L. Osheroff, *Proc. Nat. Acad. Sci. USA*, **73**, 1300-1304 (1976).
9. Z. Wide, *Acta Endocr. (Kbh.)*, **41**, Suppl. 70, 1-100 (1962).