release. These agents prevented a decrease of the RPF and mainly of the GFR and consequently protected the animals against ARF. Nevertheless, further investigation must take place and more parameters must be measured simultaneously, mainly those concerning renal circulation, the blood pressure, the release of the prostaglandin F (PGF_{2a}) (which inhibits renin release[30,31] and facilitates venous circulation[32]) and thromboxane A_2 (TXA_2) (which is a potent vasoconstrictor agent[33]).

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Enhancement of the sensitivity of hamster cheek pouch arterioles to beta-adrenergic stimulus during pregnancy

B. Zsolnai, M. Orosz and B. Varga

Departments of Obstetics and Gynecology II, and Oral Surgery, Semmelweis University Medical School, H-1082 Budapest (Hungary), and Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest (Hungary), 27 March 1981

Summary. The adrenergic beta stimulant fenoterol induced a dose-dependent vasodilatation of hamster cheek pouch arterioles. The response to fenoterol was significantly larger on day 14 of pregnancy than in metoestrous animals. Since the serum progesterone and 17 beta-oestradiol level were also elevated on day 14, a relationship was suggested between the enhancement of vascular sensitivity and sex-steroid hormone levels.

Sex-steroid treatment is able to modify the sensitivity of arterioles to catecholamines[1-4]. As the blood level of sex-steroids increases during pregnancy a change in the sensitivity of arterioles can be expected to beta-adrenergic stimulus. Thus we have studied a) whether the sensitivity of arterioles to beta-adrenergic stimulus changes during pregnancy, and b) whether the change in sensitivity is connected with the increase in sex-steroid plasma level.

Materials and methods. Golden hamsters weighing 90–140 g were maintained on 13 light and 11 dark photoperiods. The regular 4-day oestrus cycle was determined by a postovulatory vaginal discharge. $^2/_3$ of the animals were put together with fertile males on a proestrus afternoon and the following day the sperm positive females were considered as day-1 pregnant.

Microcirculatory study was performed under pentobarbital (60 mg/kg; May and Baker) anesthesia on day 6 or day 14 of the pregnancy (hamster pregnancy is 16 days); metoestrous animals served as controls. The cheek pouch membrane of animals was fixed on a special table and placed under a Zeiss microscope. In order to prevent the drying out of the membrane a small quantity of physiological saline solution was infused continuously into the cheek pouch by a peristaltic pump. Arterioles ranging in size from 30 to 60 µm were selected for study and a short-circuit television (Siemens) was applied to reach an appropiate magnification (×500–1500). Fenoterol (Partusisten, Boehringer) in doses of 0.25, 0.5 or 1.0 µg was topically applied and 20, 40 and 60 sec after its administration, the changes of the inner diameter of the arterioles was measured using a scale on the screen of the television. Then the membrane was washed out and the next dose was randomly administered 5 min later.

Following the microcirculatory study, blood was taken

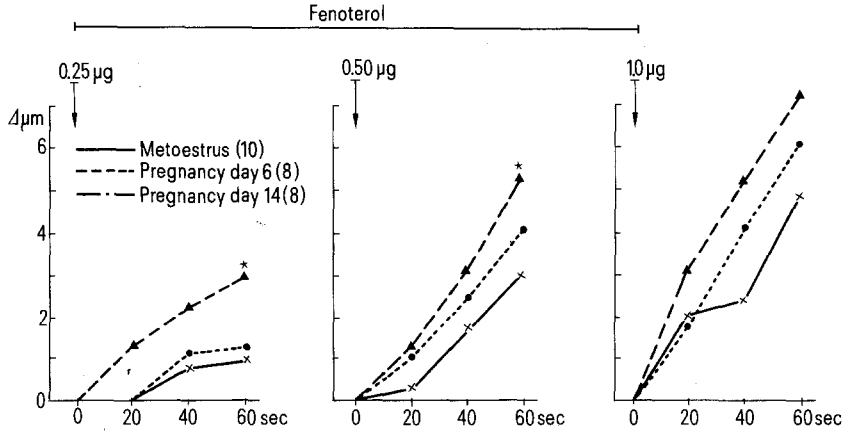

Figure 1. Net changes in arteriolar diameter 20, 40 and 60 sec after topical administration of different doses of fenoterol in metoestrous, day-6 and day-14 pregnant hamsters. Means; number of experiments in parentheses. * $p < 0.05$.

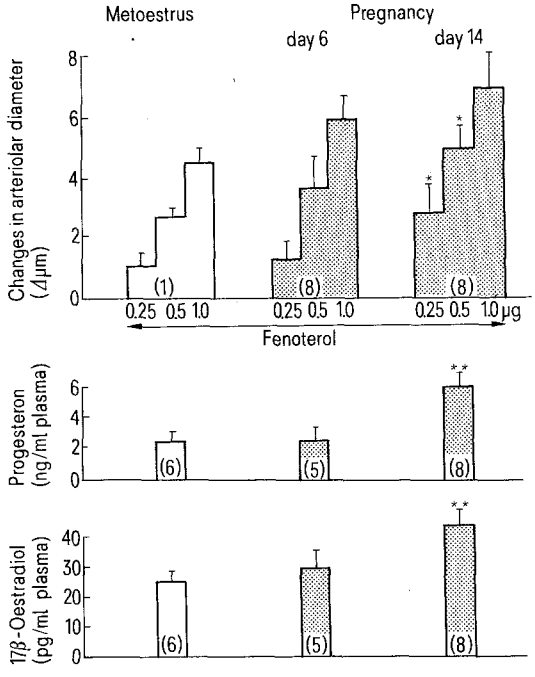

Figure 2. Arteriolar dilatation 60 sec after local administration of different doses of fenoterol in metoestrous, day-6 and day-14 pregnant hamsters and the peripheral progesterone and 17 beta-oestradiol plasma levels of the same animals. Mean ± SE, number of experiments in parentheses. * $p < 0.05$; ** $p < 0.01$.

from the aorta for progesterone[5] and 17 beta-oestradiol[6] determinations by RIA.

The net changes (Δ µm) in the inner diameter of the arterioles were calculated, progesterone and 17 beta-oestradiol plasma level was given in ng/ml or pg/ml terms, respectively. Analysis of variance and Dunnet multiple range tests were used for statistical evaluation.

Results and discussion. Fenoterol induced dose-dependent dilatation of arterioles in pregnant and non-pregnant hamsters. This arteriolar dilatation developed gradually with the passing of time. The net changes in the arteriolar diameter in day 6 and day 14 of pregnancy at all 3 doses exceeded the value obtained in the metoestrous animals. However, the difference was statistically significant in those day-14 pregnant animals which were given a 0.25- or 0.5-µg dose of fenoterol (fig. 1). The progesterone and 17 beta-oestradiol blood level also increased significantly on day 14 of the pregnancy (fig. 2).

According to our data, the sensitivity of arterioles to fenoterol increases as the pregnancy progresses, which is probably due to the elevation of the sex steroid blood level. Therefore, there seems to be a positive correlation between the increase of arteriolar sensitivity and the elevation of the progesterone and 17 beta-oestradiol blood levels.

In the pregnant uterus, progesterone increases the sensitivity of beta-adrenergic receptors to beta-mimetics[7]. In progesterone-pretreated ovariectomized hamsters the vasoconstriction induced by noradrenaline was decreased. On the other hand, in pregnant animals when the progesterone level is elevated (on day 14) an increased sensitivity was observed to noradrenaline[3]. It is also supposed that the oestrogen treatment enhances the vascular sensitivity to catecholamines[1]. The oestrogens may stimulate the release of noradrenaline from the nerve endings and prevent its being taken up again[8]. Others have observed an opposite effect[9]. It has also been pointed out that oestrogens alter the metabolism of catecholamines[10]. The question is complicated even more by the fact that the sex-steroids increase the sensitivity of arterioles to vasopressin also[1].

The experiment shows that with progression of the pregnancy, the sensitivity of arterioles to the beta-adrenergic stimulant fenoterol increases. From the clinical point of view, one must take this fact into consideration since the $beta_2$-adrenergic stimulants (like fenoterol) are widely used in the prevention of premature births. Of course, the hormone levels of women and hamsters and their local circulatory regulation can vary greatly. However, we have to take into account the possibility that the cardiovascular effects of fenoterol depend also on the peripheral sex hormone level and the usual dose of fenoterol can elicit enhanced cardiovascular effects in the later stages of pregnancy.

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