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METABOLIC CONTROL MECHANISMS IN MAMMALIAN SYSTEMS—VI

ESTROGENIC CONTROL OF UTERINE LACTATE AND α-GLYCEROPHOSPHATE PRODUCTION IN OVARIECTOMIZED RATS*

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Abstract—The regulation by estradiol-17β of lactate and α-glycerophosphate production from glucose and glucose 6-phosphate was investigated in uteri of ovariectomized rats. Time-course studies revealed that a single i.m. injection of estradiol-17β (10 μg/100g) produced statistically significant increases in lactate and α-glycerophosphate formation at 4 hr which reached peak levels at 16 hr. Both lactate and α-glycerophosphate production were enhanced after estradiol treatment to more than 200 per cent of the control values whether expressed per uterus or per mg DNA. Activities were greater with glucose 6-phosphate as substrate than with glucose indicating that glucose phosphorylation is an important rate -limiting step in the estrogenic stimulation of uterine glycolysis. The estradiol-induced increases in lactate and α-glycerophosphate production were reduced significantly by two anti estrogenic agents, nafoxidine hydrochloride (U-11100A) (50 μg/100 g) and ethamoxytriphetol (MER-25) (5 mg/100 g) as well as by progesterone (5 mg/100 g). Additionally, the administration of two anti-uterotrophic agents, actinomycin (25 μg/100 g) and cycloheximide (70 μg/100 g), resulted in almost complete inhibition of the estradiol-induced increases in the production of uterine lactate and α-glycerophosphate. The results described in this communication, along with our previous data on the estrogenic induction of several carbohydrate-metabolizing enzymes, are consonant with the suggestion that the process of estradiol-stimulated glycolysis in uterine tissue entails an increased formation of certain specific proteins.

INVESTIGATIONS into the mechanisms controlling metabolic processes in secondary sexual tissues of male and female rats revealed that sex hormones are capable of stimulating the activities of several important enzymes involved in the Embden–Meyerhof pathway of carbohydrate metabolism.[1–5] The rapid increases in phosphofructokinase and phosphohexose isomerase induced by estradiol-17β in uteri of ovariectomized rats were interpreted to represent enzyme formation *de novo* since they were blocked effectively by a variety of compounds known to exert profound inhibitory effects on RNA and protein synthesis.[1,2] Walaas *et al.*[6] postulated that the enhanced glycolysis induced by estrogens in isolated uterine muscle may have entailed

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an increase in hexokinase activity. Our recent studies on the action of estrogenic hormones as inducers of this key rate-limiting enzyme in the uterus of the ovariectomized rat provided experimental evidence for this hypothesis.[5] Inasmuch as lactate formation is considered to be an important measure of the glycolytic pathway, the present study was aimed at investigating the effects of estrogen administration on the production of lactate from glucose and glucose 6-phosphate by uterine supernatants. Additionally since estrogens are known to influence uterine lipid metabolism,[7] it was of interest to assess the effects of estradiol-17β on the production of uterine α-glycerophosphate, an important precursor for the synthesis of triglycerides. The results indicate that the formation of both lactate and α-glycerophosphate by uteri of ovariectomized rats is markedly enhanced by estradiol-17β and that the estrogen-induced stimulation of the formation of these metabolites can be inhibited by progesterone as well as by a variety of anti-uterotrophic agents.

MATERIALS AND METHODS

Animals. Female Wistar rats weighing approximately 140 g at the time of surgery were used in this study. Bilateral ovariectomies were performed and the animals were used 2 weeks postoperatively as described in previous communications.[1,2,5]

Tissue preparation and assay procedures. The preparation of uterine homogenates and supernatant fluids has been described.[1,2,5] Lactate and α-glycerophosphate production were measured under linear kinetic conditions at 37° using 0·4 ml of 5% uterine supernatant fluid in a total volume of 1·0 ml. The assay medium contained the following in their designated final concentrations: 2 mM $MgSO_4$, 2 mM ATP, 1 mM NAD, 30 mM nicotinamide, 5 mM potassium phosphate and 50 mM glycyl–glycine buffer, pH 7·4. In addition, the reaction mixture contained either glucose (100 mM) or glucose 6-phosphate (10 mM) as the substrate. Incubations were carried out for 0, 20, 40 and 60 min and the reaction terminated by the addition of 1·0 ml of 10% trichloroacetic acid. Lactate and α-glycerophosphate estimations were performed on deproteinized samples by the enzymic procedures of Hohorst.[8] The data were calculated as μmoles of lactate or α-glycerophosphate produced per hr per g of tissue and expressed either per total uterus or per mg DNA. DNA was determined on uterine homogenates essentially as described by Burton.[9] The results were subjected to statistical evaluation and the differences between the means giving a probability of less than 5 per cent were considered to be significant.

Chemicals and doses. Estradiol-17β was obtained from Sigma Chemical Co. and progesterone from Nutritional Biochemicals. Cycloheximide and nafoxidine hydrochloride (U-11100A) were kindly donated by Upjohn. Generous supplies of actinomycin D and ethamoxytriphetol (MER-25) were given, respectively, by Merck, Sharp & Dohme and William S. Merrell Co. Estradiol-17β was dissolved in ethanolic-0·9% NaCl solution and given i.m. in a single dose of 10·0 μg/100 g body weight. Progesterone (5 mg/100 g) was also solubilized in ethanolic-0·9% NaCl and injected i.m. 30 min prior to estradiol injection. Actinomycin D (25 μg/100 g) and cycloheximide (70 μg/100 g) were dissolved in 0·9% NaCl and injected i.p. 30 min before administration of the estrogen. U-11100A (50 μg/100 g) as well as MER-25 (5·0 mg/100g) were solubilized in ethanolic-0·9% NaCl and given by the i.m. route 30 min prior to estradiol injection.

RESULTS AND DISCUSSION

Effects of estradiol, progesterone and some anti-uterotrophic agents on uterine weights and DNA content. In accord with earlier observations,[2] uterine weights were increased significantly (159 per cent) at 4 hr after administration of estradiol-17β to ovariectmized rats (Table 1). The weights of the uteri increased to over 200 per cent of control values 8 to 24 hr after estradiol injection. Although DNA concentration decreased significantly after estrogen treatment, the total DNA content of the uterus remained relatively unaltered. The alterations in DNA concentration after estradiol treatment would most likely reflect changes in uterine cellular constituents rather than cell numbers since total DNA content remains practically unchanged during the entire period of the experiment. A simular conclusion may be drawn from the recent work of Hamilton *et al.*[10] Although progesterone alone exerted no significant effect on uterine weight or DNA concentration, it reduced significantly the effects of estradiol-17β on these parameters. The effects of estradiol on both uterine weight and DNA concentration were also decreased by two inhibitors of protein synthesis, actinomycin and cycloheximide. Likewise, two anti-estrogenic compounds, U-11100A and MER-25, blocked significantly the effects of estradiol-17β on uterine weight as well as the

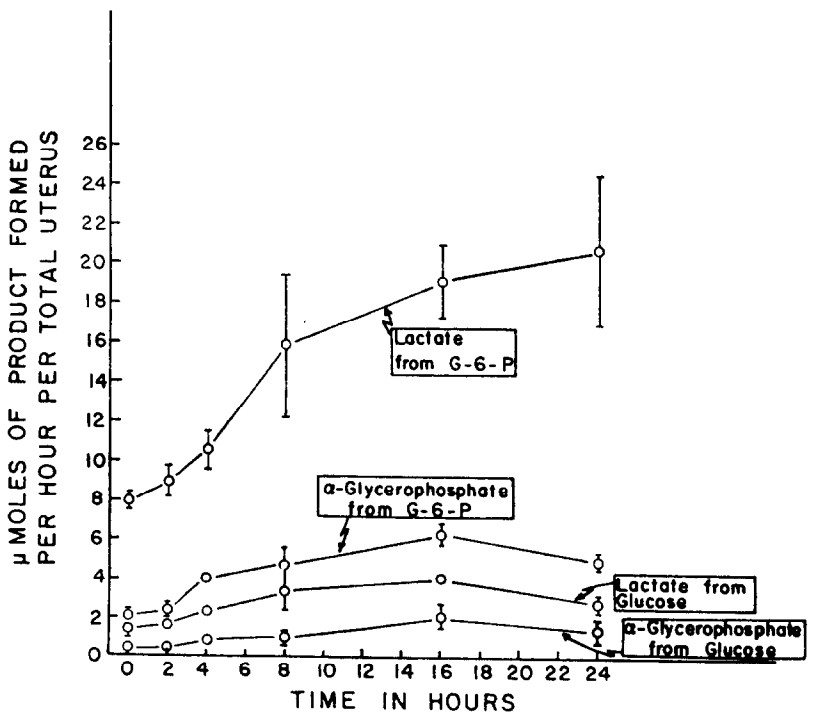

FIG. 1. Sequence of events during estradiol-induced increases in uterine lactate and α-glycerophosphate production during a 24 hr-period. Each point represents the mean ± S.E. of three values, each obtained by pooling uteri from three to four rats. Groups of ovariectomized rats were injected with estradiol-17β (10 μg/100 g) i.m. and killed at the time intervals indicated. Activities are expressed as μmoles of lactate or α-glycerophosphate formed from glucose and glucose 6-phosphate per hr per total uterus.

TABLE 1. TIME-COURSE OF ESTRADIOL-INDUCED CHANGES IN UTERINE WEIGHT AND DNA CONTENT*

Time (hr)	Uterine weight (mg)	DNA concn (mg/g uterus)	Total DNA content (mg/uterus)
Control	81 ± 5 (100)	13·8 ± 1·0 (100)	1·12 ± 0·11 (100)
2	90 ± 4 (111)	10·7 ± 0·3 (78)†	0·97 ± 0·02 (87)
4	129 ± 10 (159)†	10·1 ± 0·03 (73)†	1·31 ± 0·14 (117)
8	194 ± 49 (240)	8·9 ± 0·6 (65)†	1·66 ± 0·29 (148)
16	200 ± 7 (247)†	6·2 ± 0·5 (45)†	1·25 ± 0·13 (112)
24	202 ± 33 (250)†	7·1 ± 0·3 (51)†	1·45 ± 0·30 (129)

* Means ± S.E. represent three determinations of uterine weights or DNA content. Each value is based on uteri pooled from three to four rats. Ovariectomized rats were injected with estradiol-17β (10 μg/100 g) i.m. and sacrificed at the indicated time intervals. Data are also given in percentages (in parentheses) taking the values of control rats as 100 per cent.

† Statistically significant difference as compared with the values of control rats ($P = < 0{\cdot}05$).

TABLE 2. EFFECT OF ESTRADIOL, PROGESTERONE AND SOME ANTI-UTEROTROPHIC AGENTS ON UTERINE WEIGHT AND DNA CONTENT*

Treatment	Uterine weight (mg)	DNA concn (mg/g uterus)	Total DNA content (mg/uterus)
Control	109 ± 7 (100)	13·1 ± 0·1 (100)	1·43 ± 0·08 (100)
Estradiol	200 ± 7 (184)†	6·2 ± 0·5 (47)†	1·25 ± 0·13 (87)
Progesterone	99 ± 3 (91)	12·7 ± 1·2 (97)	1·26 ± 0·15 (88)
Estradiol-17β progesterone	144 ± 3 (132)†	11·8 ± 0·6 (90)	1·31 ± 0·04 (92)
Estradiol-17β + actinomycin	136 ± 12 (125)	10·7 ± 0·7 (82)†	1·45 ± 0·10 (101)
Estradiol-17β + cycloheximide	136 ± 4 (125)†	11·1 ± 0·4 (85)†	1·50 ± 0·01 (105)
U-11100A	122 ± 9 (112)	9·3 ± 1·4 (71)	1·11 ± 0·13 (78)
Estradiol-17β + U-11100A	129 ± 7 (118)	14·1 ± 1·7 (108)	1·83 ± 0·13 (128)
MER-25	127 ± 4 (117)	9·3 ± 0·6 (71)†	1·18 ± 0·07 (83)
Estradiol-17β + MER-25	127 + 7 (117)	10·8 ± 1·0 (82)	1·35 ± 0·06 (94)

* Means ± S.E. represent three determinations of uterine weights or DNA content. Each value is based on uteri pooled from three to four rats. Ovariectomized rats were treated by injection with estradiol-17β (10 μg/100 g) i.m. and killed after 16 hr. U-11100A (50 μg/100 g), progesterone (5 mg/100 g) or MER-25 (5 mg/100 g) were injected i.m. 30 min prior to estradiol administration. Actinomycin (25 μg/100 g) and cycloheximide (70 μg/100 g) were injected i.p. 30 min before the injection of estradiol. Data are also given in percentages (in parentheses) taking the values of control rats as 100 per cent.

† Statistically significant difference as compared with the values of control rats ($P = < 0{\cdot}05$).

concentration of DNA. None of the treatments exerted any significant effect on the total DNA content of the uterus (Table 2).

Time-course of estradiol-induced changes in lactate and α-glycerophosphate production. The sequential changes in metabolite production by uterine supernatants after a single i.m. injection of estradiol-17β are illustrated in Figs. 1 and 2. An analysis of the data, when expressed per total uterus, indicates that the earliest significant changes in the production of lactate and α-glycerophosphate are detectable at 4 hr after estradiol injection. Lactate and α-glycerophosphate production from glucose were increased to 164 and 200 per cent, respectively, when compared with their control values. At 8, 16 and 24 hr, the production of lactate was further increased to 224, 300 and 238 per cent

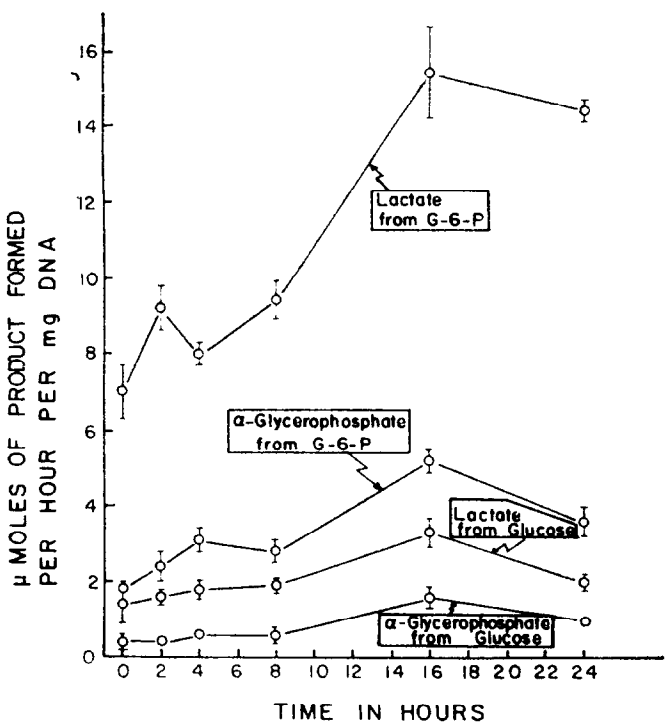

FIG. 2. Sequence of events during estradiol-induced changes in uterine glycolysis. The experimental conditions were as described in Fig. 1. Activities are expressed as μmoles of lactate or α-glycerophosphate produced per hr per mg DNA.

while that of α-glycerophosphate to 250, 525 and 375 per cent of the control values respectively. The formation of lactate from glucose 6-phosphate was elevated to 133, 200, 242 and 262 per cent, respectively, at 4, 8, 16 and 24 hr after estrogen injection. At these times, the formation of α-glycerophosphate from glucose 6-phosphate was enhanced to 191, 224, 300 and 238 per cent of the control values. The results illustrated in Fig. 2 demonstrate that a similar time-course for the production of lactate and α-glycerophosphate is obtained when the values are calculated per mg of DNA. In all

cases, maximum activities were observed 16 hr after administration of the hormone. Since absolute activities were greater with glucose 6-phosphate than with glucose, the data indicate that under the conditions examined, the phosphorylation of glucose may be a rate-limiting step for the production of both lactate and α-glycerophosphate. As lactate formation is considered to be a reliable measure of the Embden–Meyerhof pathway, the presently observed increased yields of this metabolite suggest that energy production in the uterus is augmented under the influence of estrogens. The observed increases in α-glycerophosphate production by uterine preparations of estradiol-treated rats would appear to provide support for the observations of Mueller *et al.*[7] on the enhanced synthesis of phospholipids after estrogen treatment.

Action of anti-estrogenic compounds on estradiol-induced changes in uterine glycolysis. Since U-11100A and MER-25 apparently compete with estradiol-17β for specific receptor sites in uterine tissue,[11] studies were undertaken to examine whether these anti-estrogens were capable of blocking the action of estradiol-17β on uterine lactate and α-glycerophosphate production. The dose levels of the anti-estrogens employed in this study were those shown by Jensen[11] to inhibit the uptake and retention of estradiol-17β by uterine tissue. The results presented in Table 3 show that the administration of U-11100A (50 μg/100 g) or MER-25 (5 mg/100 g) either blocked or significantly reduced the increases in lactate and α-glycerophosphate production observed after estradiol injection. The inhibitory effects of these antiestrogenic agents were observed with both glucose and glucose 6-phosphate as substrates. When U-11100A or MER-25 was administered alone, either no significant effect or a weak stimulatory action was noted.

Effects of antinomycin and cycloheximide on estradiol-induced enhancement in lactate and α-glycerophosphate production by rat uteri. Previous studies suggested that the estrogenic induction of uterine hexokinase, phosphohexose isomerase and phosphofructokinase may represent enzyme synthesis *de novo* involving stimulation of the synthesis of certain RNA species.[1,2,5] These conclusions were derived from experiments wherein the estrogen-induced increases in the activities of these glycolytic enzymes were effectively blocked by several compounds known to inhibit RNA and protein synthesis either directly or indirectly.[1,2,5] The inhibitory effects of such compounds on estrogen-induced changes in RNA and protein synthesis have been well documented.[7,12–14] It was of interest, therefore, to examine the effects of actinomycin and cycloheximide on the estradiol-augmented increases in the production of uterine lactate and α-glycerophosphate. The increased formation of these two metabolites in uteri of rats subjected to estradiol treatment was inhibited significantly by actinomycin and cycloheximide (Table 4). Although the possibility of non-specific toxic effects requires some caution in the interpretation of the results,[15] the inhibition of the estradiol-stimulated increases in the production of lactate and α-glycerophosphate by actinomycin and cycloheximide lends support to our previous studies on the action of estrogenic hormones as inducers of several uterine enzymes involved in the process of glycolysis.[1,2,5]

Action of progesterone on lactate and α-glycerophosphate production. The effects of progesterone on the estradiol-stimulated biochemical processes in the uterus vary with the dose of progesterone given.[16] In the present study, the dose of progesterone utilized (5 mg/100 g) was that which was shown to prevent effectively the estradiol-induced increases in the activities of certain uterine enzymes involved in the glycolytic

TABLE 3. EFFECTS OF ESTRADIOL-17β AND TWO ANTI-ESTROGENIC COMPOUNDS ON LACTATE AND α-GLYCEROPHOSPHATE PRODUCTION BY RAT UTERI*

Product:	Lactate				α-Glycerophosphate			
Substrate:	Glucose		Glucose 6-phosphate		Glucose		Glucose 6-phosphate	
Rate:	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA
Treatment								
Control	1·4 ± 0·5 (100)	1·4 ± 0·5 (100)	7·9 ± 0·5 (100)	7·0 ± 0·7 (100)	0·4 ± 0·3 (100)	0·4 ± 0·3 (100)	2·1 ± 0·3 (100)	1·8 ± 0·1 (100)
Estradiol-17β	4·1 ± 0·1 (293)†	3·3 ± 0·4 (236)†	19·1 ± 1·9 (242)†	15·4 ± 1·2 (220)†	2·1 ± 0·6 (525)	1·6 ± 0·3 (400)	6·3 ± 0·5 (300)†	5·2 ± 0·3 (289)†
U11100A	2·1 ± 0·1 (150)	2·0 ± 0·2 (143)	11·5 ± 0·5 (146)†	10·4 ± 0·7 (149)†	0·5 ± 0·2 (125)	0·5 ± 0·2 (125)	0·5 ± 0·2 (119)	2·3 ± 0·2 (128)
Estradiol-17β + U11100A	1·7 ± 0·1 (121)	1·0 ± 0·1 (71)	11·4 ± 1·1 (144)†	6·3 ± 0·8 (90)	0·8 ± 0·1 (200)	0·5 ± 0·1 (125)	3·4 ± 0·1 (162)†	1·9 ± 0·2 (106)
MER-25	2·0 ± 0·3 (143)	1·7 ± 0·3 (121	13·6 ± 2·1 (172)	11·4 ± 1·5 (163)	0·7 ± 0·2 (175)	0·6 ± 0·2 (150)	3·2 ± 0·3 (152)	2·7 ± 0·3 (150)†
Estradiol-17β + MER-25	2·9 ± 0·5 (207)	2·1 ± 0·4 (150)	13·6 ± 1·7 (172)	10·2 ± 1·5 (146)	1·0 ± 0·2 (250)	0·7 ± 0·1 (175)	2·5 ± 0·5 (119)	2·1 ± 0·4 (117)

* Means ± S.E. represent three determinations of lactate or α-glycerophosphate production. Each assay was carried out in uteri pooled from three to four rats. Ovariectomized rats were treated by injection with estradiol-17β (10 μg/100 g) i.m. and killed after 16 hr. U11100A (50 μg/100 g) and MER-25 (5 mg/100 g) were also injected i.m. 30 min prior to estradiol administration. Data are also given in percentages (in parentheses) taking the values of control rats as 100 per cent.

† Statistically significant difference as compared with the values of control rats ($P = < 0·05$).

TABLE 4. EFFECTS OF TWO INHIBITORS OF PROTEIN SYNTHESIS ON ESTRADIOL-INDUCED CHANGES IN LACTATE AND α-GLYCEROPHOSPHATE PRODUCTION BY RAT UTERI*

Product:	Lactate				α-Glycerophosphate			
Substrate:	Glucose		Glucose 6-phosphate		Glucose		Glucose 6-phosphate	
Rate:	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA	μmoles/hr/ uterus	μmoles/hr/ mg DNA
Treatment								
Control	1·8 ± 0·1 (100)	1·3 ± 0·1 (100)	11·5 ± 0·4 (100)	8·1 ± 0·3 (100)	0·5 ± 0·1 (100)	0·4 ± 0·1 (100)	2·0 ± 0·1 (100)	1·4 ± 0·2 (100)
Estradiol-17β	4·1 ± 0·1 (228)†	3·3 ± 0·4 (254)†	19·1 ± 0·4 (166)†	15·4 ± 1·2 (190)†	2·1 ± 0·6 (420)	1·6 ± 0·3 (400)†	6·3 ± 0·5 (315)†	5·2 ± 0·3 (371)†
Estradiol-17β + actinomycin	2·4 ± 0·0 (133)†	1·8 ± 0·1 (138)	13·6 ± 2·1 (118)	9·1 ± 1·3 (112)	1·1 ± 0·2 (220)	0·8 ± 0·1 (220)†	3·6 ± 0·6 (180)	2·5 ± 0·3 (179)†
Estradiol-17β + cycloheximide	2·2 ± 0·2 (122)	1·5 ± 0·2 (115)	12·6 ± 0·6 (109)	8·6 ± 0·3 (106)	0·8 ± 0·2 (160)	0·6 ± 0·1 (150)	3·3 ± 0·1 (165)†	2·0 ± 0·0 (143)†

* Means ± S.E. represent three determinations of lactate or α-glycerophosphate production. Each assay was carried out in uteri pooled from three to four rats. Ovariectomized rats were treated by injection with estradiol-17β (10 μg/100 g) i.m. and killed after 16 hr. Actinomycin (25 μg/100 g) and cycloheximide (70 μg/100 g) were injected i.p. 30 min before administration of estradiol. Data are also given in percentages (in parentheses)taking the values of control rats as 100 per cent.

† Statistically significant differences as compared with the values of control rats ($P = < 0·05$).

pathway.[1,2] The results presented in Fig. 3 demonstrate that progesterone alone exerted no significant effect on lactate production with either glucose or glucose 6-phosphate as the substrate. When ovariectomized rats were treated withh estradiol-17β (10 μg/100 g), lactate production was increased to more than 200 per cent of the

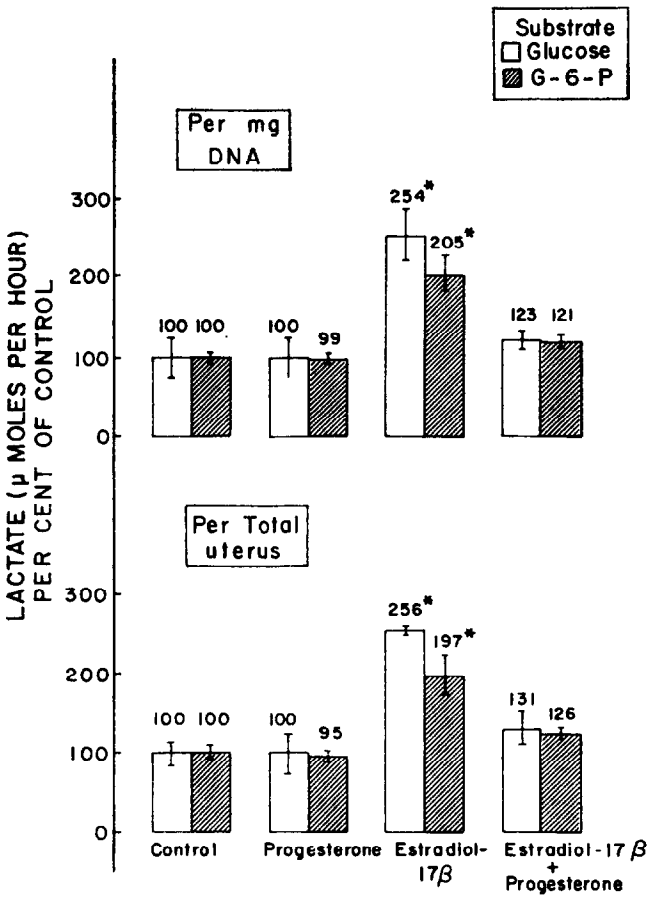

FIG. 3. Effects of progesterone on estradiol-stimulated lactate production by uterine supernatants. Bars represent the mean and S.E. of three values, each obtained by pooling uteri from three to four rats. Ovariectomized rats were treated by injection with estradiol-17β (10 μg/100 g) i. m., and killed after 16 hr. Progesterone (5 mg/100 g) was also given i.m. 30 min prior to estradiol administration. Data are given in percentages taking the values of control rats as 100 per cent. *Statistically significant difference as compared with the values of control animals ($P = < 0{\cdot}05$).

control values when calculated per mg of DNA or per total uterus. Pretreatment of estradiol-injected animals with progesterone resulted in activities which were not significantly different from those of the control values. The effects of progesterone on the estradiol-stimulated formation of α-glycerophosphate were similar to those observed for lactate production (Fig. 4). Whereas progesterone alone had little or no effect, the estradiol-induced increases in α-glycerophosphate formation were blocked effectively by this hormone. Since progesterone has been shown to inhibit the estradiol-stimulated increases in uterine phosphofructokinase and phosphohexose isomerase,

the present results are in accord with our earlier suggestion that the action of estradiol as an inducer and of progesterone as a suppressor of uterine enzyme biosynthesis may be important in the maintenance of homeostatic mechanisms involved in uterine glucose metabolism.[1,2]

The data obtained in the present investigation substantiate our earlier findings on the induction of uterine glycolytic enzymes by estrogenic hormones.[1,2,5] Since the early

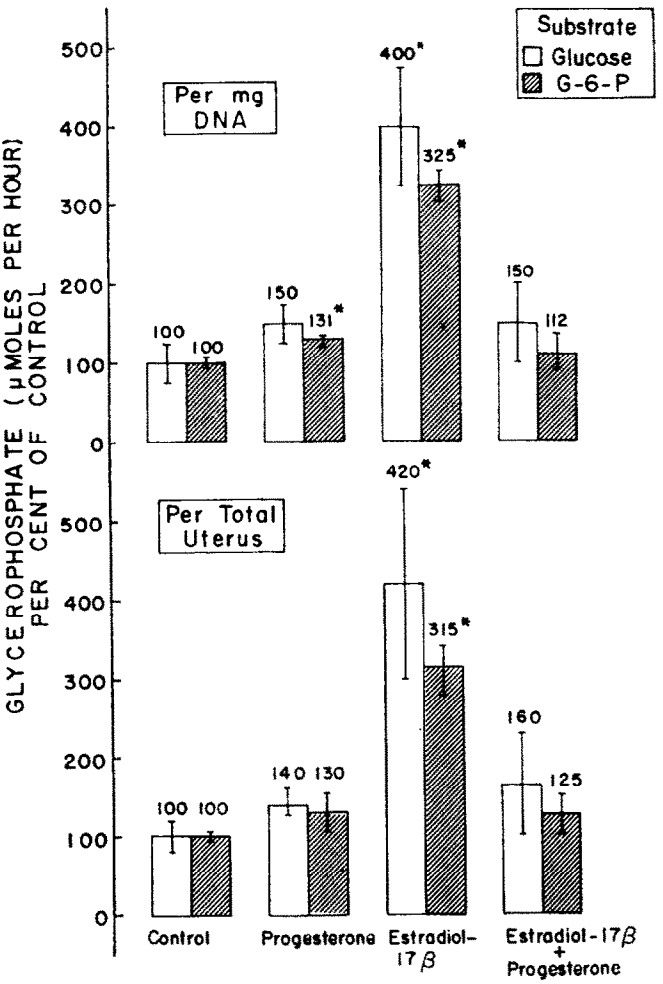

FIG. 4. Effects of progesterone on estradiol-induced increased in uterine α-glycerophosphate production. Experimental conditions were as described in Fig. 3. Data are given in percentages taking the values of control animals as 100 per cent. *Statistically significant difference as compared with the values of control rats ($P = < 0{\cdot}05$).

studies of Cori,[17] evidence has accumulated which indicates that the step involving the conversion of glucose to glucose 6-phosphate may be rate-limiting for the process of glycolysis in many tissues. In the present study, the greater yields of lactate and α-glycerophosphate from glucose 6-phosphate than from glucose as the substrate provides evidence for the rate-limiting role of hexokinase in uterine tissue. Since

increases in lactate and α-glycerophosphate production were seen with uteri of estradiol-treated rats when either glucose of glucose 6-phosphate was the substrate, the data suggest that estrogens must influence, in addition to hexokinase, other key enzymatic steps involved in the glycolytic chain of events. Since estrogens have been shown to induce the biosynthesis of uterine phosphofructokinase,[1] and more recently that of aldolase and pyruvate kinase (unpublished work), the results are consonant with the view that estrogenic hormones regulate uterine glucose metabolism by affecting several key rate-limiting steps simultaneously.

Jensen demonstrated that the two anti-estrogens, U-11100A and MER-25, inhibit the uptake and retention of tritiated estradiol by uterine and vaginal tissues thus competing with estradiol for receptor sites. The marked inhibition of the estradiol-stimulated increases in the production of lactate and α-glycerophosphate from glucose and glucose 6-phosphate by U-11100A and MER-25 provides additional evidence for the anti-estrogenicity of these synthetic compounds in the uterus. Jensen[11] further showed that in contrast to the anti-estrogens, actinomycin and puromycin exert their anti-uterotrophic effects by acting at stages subsequent to the initial association of estradiol with the receptors. Antinomycin, which inhibits the synthesis of messenger-RNA by binding to the deoxyguanosine bases of DNA,[18] and cycloheximide, which is believed to suppress protein synthesis by inhibiting the transfer of amino-acyl transfer RNA to ribosomes,[19,20] have indeed been demonstrated to block the estradiol-stimulated increases in RNA and protein synthesis in the uterus.[12–14] Since these antibiotics are also capable of diminishing the effects of estradiol-17β on the formation of uterine lactate, α-glycerophosphate, as well as certain glycolytic enzymes, the data are in accordance with the suggestion that the estradiol stimulation of uterine glycolysis entails the formation of certain specific proteins.

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