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ROLE OF PROSTAGLANDIN E_2 IN ALTERATIONS OF THE β-ADRENERGIC SYSTEM FROM RAT ECLAMPTIC UTERUS

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Abstract—The inotropic effect of isoproterenol, as well as the β-adrenoceptor population, was measured in pregnant uterine tissue from female spontaneous hypertensive rats (SHR) (control group: C) and female SHR that were grafted with skin from Holtzman male rats (eclamptic group: E). The K_d value of the concentration–response curve of isoproterenol was higher for uteri from E rats than C rats. This phenomenon was not accompanied by a modification in the expression of β-adrenoceptors. Inhibition of the synthesis of prostaglandins prevented the hyporeactivity to isoproterenol during eclampsia. Moreover, uteri from E rats generated and released greater amounts of prostaglandin E_2 (PGE_2) than uteri from C rats, even in the presence or absence of isoproterenol. In addition, whereas isoproterenol administered alone increased basal cyclic AMP (cAMP) production from C uteri, PGE_2 administered alone enhanced cAMP production in E uterine tissue. These results suggest that the decrease in β-adrenergic response to the agonist in E rats is ascribed to PGE_2 production. The abnormal reactivity to the β-agonist could be associated with a heterologous desensitization of uterine β-adrenoceptors exerted by PGE_2 overload in uteri from E rats. These results bear directly on the regulation of uterine motility during pregnancy, since an impaired response to β-adrenergic innervation could lead to increased uterine motility, impairing the maintenance of pregnancy.

Key words: β-adrenoceptors; PGE_2; cAMP; eclamptic uterus binding assay; uterine contractility; pregnancy

In recent years, it has been of great interest to elucidate the immunopathologic mechanisms that are implicated in the generation of eclampsia. This disorder of pregnancy, which is characterized by hypertension, proteinuria, edema, abnormalities in the contractile activity of the myometrium and, at times, coagulation and/or liver abnormalities, complicates one in ten pregnancies [1].

In 1968, Chesley *et al.* [2] described eclampsia as the disease of theories, because there are several factors involved in its etiology, e.g. immunological, neuroendocrinological and hormonal.

In previous work [3, 4], we investigated changes in uterine β-adrenergic expression and PGE_2† production in relation to the presence of fetal allogeneic stimulation during normal pregnancy. Other authors have described a diminished response to β-adrenergic stimulation in hypertensive disease [5, 6].

Taking into account that uterine quiescence (which is mediated, in part, by activation of the β-adrenergic system) is necessary to maintain gestation and to allow fetal maturation, since a diminished or impaired response to β-adrenergic innervation could be interpreted as leading to increased uterine motility, which is a risk to pregnancy, we decided to investigate uterine β-adrenergic response in our experimental model of eclampsia developed in SHR.

MATERIALS AND METHODS

Animals

Virgin female inbred SHR (maximal blood pressure 150–180 mm Hg) and Holtzman inbred male rats were used throughout. All animals were 80- to 90-days-old. Female SHR (the eclamptic group: E) were grafted with skin from Holtzman males under general anesthesia; the skin was attached with 9-mm metal wound clips in a bed of a proper size on the back of the SHR recipient. The time interval between the four sequential grafts was 10 days. The breeding experiment was performed 10 days after the last graft. Each SHR was mated in proestrus in a separate cage with its corresponding skin donor. The day on which a vaginal plug was found was designated as day 1 of pregnancy. The control group (C) was composed of female SHR that were mated with Holtzman male rats but had no skin grafts. Most animals of the E group showed alterations in the number of offspring, abortions and growth delay in comparison with the C group (Table 1).

The eclamptic state was evaluated by studying renal function. Table 2 shows comparative urinary volumes and creatinine clearance from the E and C groups. It can be seen that both parameters increased normally during week 2 of pregnancy (physiological increase of glomerular filtration) and decreased during week 3. On the other hand, neither urinary volume nor creatinine clearance from the E group increased, showing a lack of adaptation of glomerular filtration during pregnancy.

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† Abbreviations: PGE_2, prostaglandin E_2; DHA, dihydroalprenolol; cAMP, cyclic AMP; SHR, spontaneous hypertensive rats; E, eclamptic; C, control; KRB, Krebs–Ringer–bicarbonate; PLA_2, phospholipase A_2; IDT, isometric developed tension; FC, frequency of contractions; FA, functional activity; and BPB, *p*-bromophenacyl bromide.

Table 1. Alterations observed in pregnant SHR with or without skin graft

	SHR with Holtzman skin graft (E)*	SHR non-grafted (C)*
Total number of rats	48	20
Total number of pregnancies	34	18
Total number of offspring	182	96
Abortions	28	0
Stillborn fetuses or death within 6 hr	28	0
Growth delay	10	0

* E = eclamptic; C = control.

Renal histology showed lesions corresponding to disseminated intravascular coagulation (data not shown).

Uterine tissue preparations

Pregnant animals from the E and C groups were decapitated on day 20 of pregnancy. The entire uterus was immediately removed, trimmed of fat and peritoneal structures, and placed in gassed (95% O_2 and 5% CO_2) Krebs–Ringer–bicarbonate (KRB) solution, the composition of which is reported elsewhere [7]. Fetus and placenta were separated carefully. Uterine horns were opened longitudinally, implantation zones were removed, and a 0.5 cm long by 0.1–0.2 cm cross-section strip was cut from between the ovarian and the cervical regions of each one; the strip was mounted in a 15-mL organ bath containing KRB glucose solution at 37°, pH 7.4, and gassed with 95% O_2 and 5% CO_2. The strips were taken from the same region of the uterus, and only one strip from each rat was used for the experiment. One end of the strip was attached to a fixed hook, and the other was connected to a force transducer coupled to an ink-writing oscillographic recorder; a basal resting tension of 500–1000 mg was applied to the preparations by means of a micrometric device, and the strips were contracted isometrically. The magnitude of basal tension was obtained by calibrating the output of the force-transducer with a fixed weight of 500 mg. Previous experiments demonstrated that the maximal contractile tension was obtained with a preload of 500–1000 mg [7, 8]. For rigorous analysis of the length/tension relationship, one muscle strip was used for length/tension and the other homologous contralateral strip from the same rat was used for the experiment. With this arrangement, the system was in condition for the recording of isometric developed tension (IDT), expressed in milligrams of wet weight tissue, and the frequency of contractions (FC), expressed as the number of contractions during a period of 10 min. The product of these two parameters (mean IDT · mean FC) at a constant resting tension was calculated in arbitrary units of functional activity (FA), as proposed elsewhere [9]. Control values (100%) refer to FA before drug additions. The absolute values of FA (mg/mg wet wt/min ± SEM) recorded after an equilibration period (60 min) were 1250 ± 95 and 1300 ± 87 for uterine strips from E and C rats, respectively. Subsequently, the FA values were compared with the corresponding control values. Cumulative concentration–response curves for isoproterenol, methoxamine, and PGE_2 on uterine strips from E and C rats were obtained according to the method of Van Rossum [10]. The time interval between each concentration was that required to produce the maximal effect (E_{max}).

Binding assay

Microsomal fractions of uterine membranes from E and C groups were prepared essentially as described by Berg *et al.* [11], Bottari *et al.* [12] and Sales *et al.* [13]. Uterine tissue was mixed in 4 vol. of cold buffer containing 0.25 M sucrose, 5 mM Tris–HCl and 1 mM $MgCl_2$, pH 7.4, and was homogenized three times with a Polytron PT 20 at a setting of 3–5 each time for 30 sec. The homogenate was filtered through four layers of gauze and spun at 700 *g* for 15 min, at 10,000 *g* for 15 min, and at 40,000 *g* for 30 min. The pellet was resuspended in 2.5 mL of 50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$. Membrane protein concentration (2–5 mg/mL) was determined by the method of Lowry *et al.* [14]. The activity of 5′-nucleotidase indicates the degree of purity of the microsomal fraction [15]. Briefly, the activity of 5′-nucleotidase was assayed by measuring the release of P_i from AMP over 30 min at 37° in a medium containing 10 mM $MgSO_4$, 50 mM glycine (pH 9.1), 5 mM AMP (pH 7.0), and water in a volume ratio of 1:2:1:5. The reaction was stopped with 8% trichloroacetic acid, and the liberated P_i was determined. The specific activity of the plasma membrane marker was: 3.8 ± 0.27 and 3.4 ± 0.22 μmol/mg protein/10 min (mean ± SEM, N = 5) in E and C tissue, respectively.

Binding of [^{3}H]DHA to uterine membranes was performed as described previously [13]. Briefly, aliquots of the membrane fractions (200 μg protein) were suspended (in duplicate) with shaking in 150 μL of assay buffer (50 mM Tris–HCl, 10 mM $MgCl_2$, pH 7.4) and incubated with increasing concentrations of [^{3}H]DHA (0.3 to 3 nM) (Amersham Int.; sp. act. 73 Ci/mmol). Incubation was stopped via rapid vacuum filtration with 2 mL of ice-cold buffer, dried, transferred to 10 mL of Triton–toluene-based scintillation fluid, and counted. Non-specific binding was defined as binding in the presence of 10 μM propranolol, never exceeding 10% of specific binding. Results were expressed as femtomoles of [^{3}H]DHA specifically bound per milligram of protein.

cAMP

Uterine strips from the E and C groups were immediately removed after the rats were killed, weighed, and incubated with spontaneous activity in 1 mL of KRB with 1 mM 3-isobutyl-1-methylxanthine, gassed with 5% CO_2 and 95% O_2 with shaking at 37° in the presence or absence of 10^{-6} M propranolol or 10^{-6} M indomethacin (15 min),and then left for 3 min more with or without 3×10^{-7} M isoproterenol or 10^{-7} M PGE_2. In all cases, the total incubation time (30 min) was the same for all experimental conditions. Tissues were then homogenized in 2 mL of ethanol and centrifuged at 2500 *g* for 15 min at 4°. The supernatants were collected, and pellets were homogenized in 1 mL of ethanol:water (2:1) and centrifuged. Supernatants were combined and evaporated at 55° under a nitrogen stream. cAMP residue was dissolved in 2 mL of assay buffer (50 mM Tris–HCl, 8 mM theophylline, 6 mM 2-mercaptoethanol, 0.45 mM EDTA, pH 7.4) and stored at –20° until the assay was

Table 2. Renal function of rats from eclamptic (E) and control (C) groups

Group	Pre-graft (basal)	Inter-graft	Week of pregnancy 1	2	3
			Urine volume (mL/24 hr)		
C	4.2 ± 2.1		4.2 ± 1.4	11.6 ± 1.9*	5.9 ± 0.9†
E	8.4 ± 2.1	6.1 ± 0.4	7.9 ± 1.2	9.5 ± 1.5	9.5 ± 2.1
			Creatinine clearance (mL/min)		
C	0.7 ± 0.2		1.3 ± 0.2*	1.8 ± 0.3‡	1.0 ± 0.2
E	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

Values are means ± SEM of 34 rats in the E group and 16 rats in the C group.
* $P < 0.01$ vs C basal.
† $P < 0.05$ vs 2nd week.
‡ $P < 0.05$, C vs E.

carried out. Aliquots of 50 μL were taken for nucleotide determination using a radioimmunoassay procedure with [^{3}H]cAMP (Amersham Int.; sp. act. 31.1 Ci/mmol) and cAMP (Sigma Chemical Co.) following the method of Brown *et al.* [16]. cAMP values were expressed in picomoles per milligram of wet weight tissue.

PGE_2 assay

The PGE_2 assay was performed in uterine tissue obtained from E and C rats following methods described previously [4]. Uteri from E and C pregnant rats at term were removed and trimmed of fat and peritoneal structures; uterine horns were opened longitudinally, and placental and fetal structures were removed. Then 1-cm uterine strips were incubated in 2 mL of KRB solution for 90 min at 37° in a Dubnoff incubator. Supernatant fractions were frozen at −70° until the PGE_2 assay was carried out. Uterine PGE_2 production was determined by a radioimmunoassay procedure following previous methods [17]. Briefly, 100 μL of samples or standards was mixed with 500 μL of anti-PGE_2 antiserum (Sigma Chemical Co.) developed in rabbits. Then, 100 μL (5.0 pg) of [^{3}H]PGE_2 (New England Nuclear; sp. act. 154.0 Ci/mmol) was added to each tube. All dilutions were done in 0.01 M PBS, pH 7.4, containing 0.1% bovine serum albumin and 0.1% sodium azide. After incubation, a dextran-coated charcoal suspension was added to separate the bound from the free fractions. The supernatants were removed from each tube, and scintillation fluid was added to determine the amount of radioactivity present. Results were expressed in picograms of PGE_2 per milligram of wet weight tissue.

Chemicals

Freshly prepared solutions in bidistilled water of the following drugs were used: isoproterenol, propranolol, acetylsalicylic acid, indomethacin, BPB, PGE_2 and verapamil (Sigma Chemical Co.). All concentrations quoted in the text represent the final values in all assays.

Statistical analysis

Student's *t*-test for unpaired values was used to determine the level of significance. Differences between means were considered significant if $P < 0.05$. Receptor concentration was determined by Scatchard analysis. Statistics of the binding assay were determined using a simple computer program for one kind of non-interacting binding sites for Scatchard plot analysis [18].

RESULTS

Contractile assay

The contractile effects of the α-adrenergic agonist (methoxamine) and the β-adrenergic agonist (isoproterenol) in isolated uteri from E and C rats were characterized. Figure 1 shows the effects of increasing concentrations of isoproterenol (A) and methoxamine (B) on the tension of uteri from C and E rats. It can be seen that methoxamine induced an increase in FA while isoproterenol decreased it in both groups. The stimulatory effect of the α-agonist was similar in both E and C rats; however, the concentration-response curve of the β-agonist was shifted to the right in uterine tissue from E rats compared with that from C rats. Prazosin and propranolol antagonized, in a competitive manner, the positive effect of methoxamine and the negative effect of isoproterenol, respectively (data not shown).

To determine the nature of the mechanism triggering the hyposensitivity to isoproterenol in uterine strips from E rats, several inhibitors acting on different pathways of the oxidative metabolism of arachidonic acid were used. As shown in Table 3 and Fig. 2, the inhibition of PLA_2 with BPB, or of the cyclooxygenase activity with aspirin or indomethacin, shifted to the left the concentration-response curve of isoproterenol on uteri from the E group, reaching values similar to those observed in uteri from rats of the C group.

To elucidate which products from the cyclooxygenase pathway could be involved in the hyposensitivity to isoproterenol observed in uteri from E rats, tissues were exposed to a subthreshold concentration of PGE_2 (10^{-8} M). Figure 2 shows that PGE_2 attenuated the maximal inhibitory effect of isoproterenol, shifting to the right the concentration-response curve on uterine strips from E rats previously exposed to indomethacin. None of the inhibitors modified the action of isoproterenol on uteri from group C rats (Table 3 and Fig. 2B). In addition, PGE_2 demonstrated a lack of action in the same group (Fig. 2B).

The reactivity to PGE_2 was also altered in uteri from the E rats. It can be seen in Fig. 3 that PGE_2 induced a concentration-dependent increase in tension of uteri from E rats, but it had no effect on the C group in the

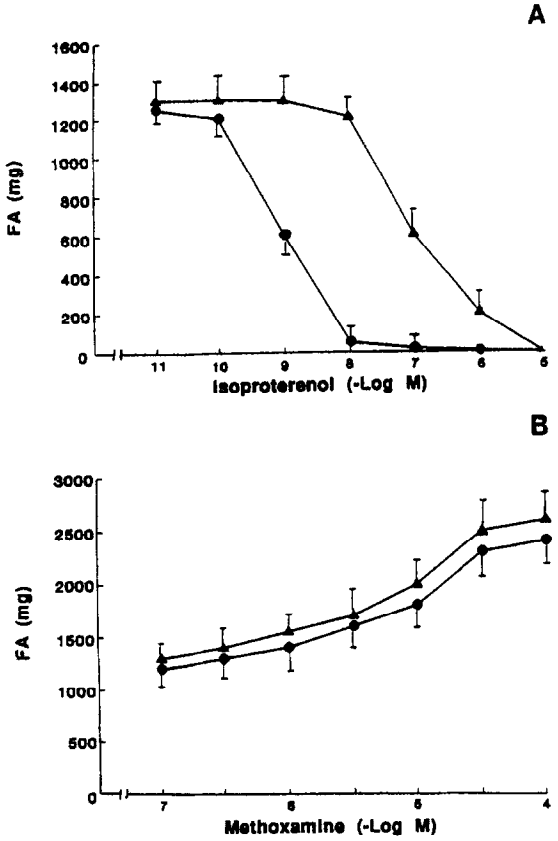

Fig. 1. Cumulative concentration–response curves of isoproterenol (A) and methoxamine (B) on isolated uterine tissue from control (C, ●—●) and eclamptic (E, ▲—▲) rats. All values are means ± SEM of 8 experiments performed in each experimental group, using one rat for each experiment. The effective concentration causing 50% of the maximal response (K_d) was: for isoproterenol: E, $2.3 \pm 0.2 \times 10^{-7}$ M and C, $1.2 \pm 0.1 \times 10^{-9}$ M (statistical difference of isoproterenol effect between the E and C groups, $P < 0.0001$); and for methoxamine: E, $8.7 \pm 0.3 \times 10^{-6}$ M and C, $9.1 \pm 0.4 \times 10^{-6}$ M. All values of functional activity (FA) are expressed in mg/mg wet wt tissue/min.

concentration range that was tested. PGE_2 increased by 160 ± 28% the FA of uteri from E rats, while an increase of 26 ± 13% was observed in FA of the C group.

PGE_2 assay

To verify if PGE_2 is involved in the effect of isoproterenol on uteri from E rats, PGE_2 release was measured in tissues from group E and C rats in the absence of presence of isoproterenol (3×10^{-7} M). Table 4 shows that uteri from both E and C rats were able to generate PGE_2, but the amount of PGE_2 was significantly higher in the supernatant fractions from E than from C uterine tissue. Inhibition of cyclooxygenase activity prevented the release of PGE_2 by E and C uteri (data not shown). In the presence of isoproterenol, the release of PGE_2 was greater in E than in C uteri. The stimulatory effect of isoproterenol upon PGE_2 release was abrogated by specific β-adrenergic blocker agents. Verapamil also inhibited the release of PGE_2 induced by isoproterenol (Table 4).

cAMP assay

To investigate the mechanism by which the inotropic effect of isoproterenol is diminished in uteri from E rats,

Table 3. Influence of inhibitors of phospholipase A_2 and cyclooxygenase on the effect of isoproterenol in uteri from control (C) and eclamptic (E) groups of rats

Drugs	K_d ($\times 10^{-9}$ M) (C)	N*	K_d ($\times 10^{-9}$ M) (E)	N*
ISO	1.2 ± 0.1	8	230 ± 21†	9
ASA + ISO	1.5 ± 0.2	7	1.2 ± 0.1	6
BPB + ISO	1.3 ± 0.1	6	1.4 ± 0.2	8

Uterine strips were exposed for 20 min to various concentrations of isoproterenol (ISO) in the absence or presence of enzymatic inhibitors: aspirin (ASA, 10^{-4} M) and *p*-bromophenacyl bromide (BPB, 10^{-6} M). Values are means ± SEM, and they were obtained using the Michaelis-Menten equation, taking linear relationships and fitting the equivalent to Lineweaver-Burk plots.

* Number of experiments performed.

† $P < 0.001$, ISO E vs C.

cAMP production was measured in the presence of isoproterenol and PGE_2 under E and C conditions. It can be see in Table 5 that basal cAMP production was higher in E than in C rats. Isoproterenol administered alone in-

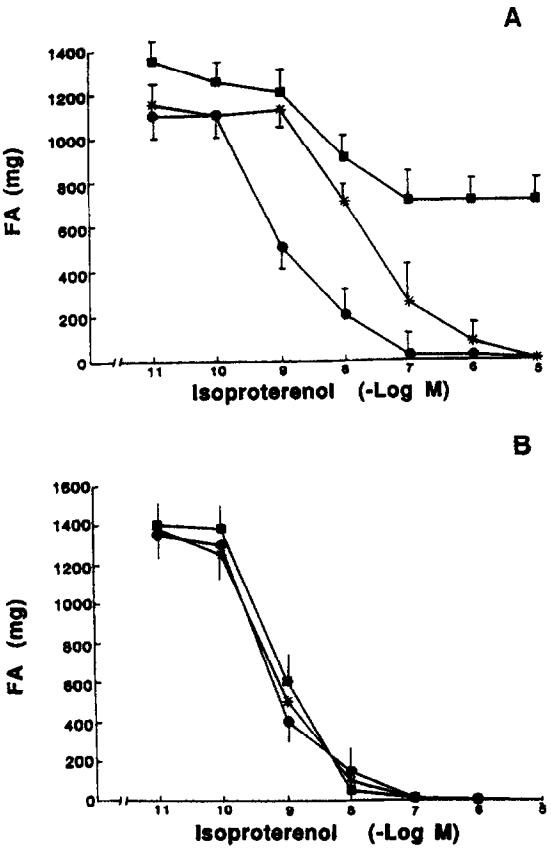

Fig. 2. Effect of isoproterenol on spontaneous motility of isolated uteri from eclamptic (A) and control (B) rats. Uterine strips were exposed to different concentrations of isoproterenol in the absence (*—*) or in the presence of 10^{-6} indomethacin (●—●), or in the presence of 10^{-6} M indomethacin plus 10^{-8} M PGE_2 (■—■). Values are means ± SEM of 5 independent experiments, using one rat for each experiment. All values of functional activity (FA) are expressed in mg/mg wet wt tissue/min.

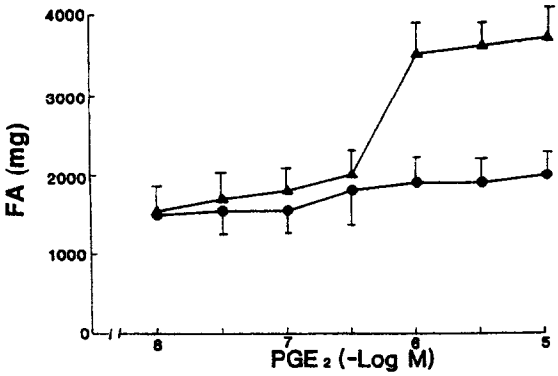

Fig. 3. Cumulative concentration–response curve of PGE_2 on isolated uterine tissue from eclamptic (▲—▲) and control (●—●) rats. All values are means ± SEM of 6 experiments performed in each experimental group, using one rat for each experiment. All values of functional activity (FA) are expressed in mg/mg wet wt tissue/min.

creased the basal production of cAMP by uteri from the C group, an effect that was blocked to propranolol and was not altered by indomethacin. On the other hand, PGE_2 administered alone enhanced production of cAMP in uterine tissue from E rats, an action that was not blunted by propranolol (Table 5).

Binding assay

To determine if the alteration in the function of β-adrenoceptors observed in uteri from E rats was accompanied by a modification of β-adrenoceptor expression, [^{3}H]DHA binding to uterine membranes was studied under E and C conditions. As shown in the upper panel of Fig. 4, [^{3}H]DHA specifically bound to uterine membrane preparations from E and C groups without a significant difference between them. Scatchard analysis of the saturation data demonstrated that there were no differences in the maximal number of binding sites (B_{max}) or in the dissociation constant (K_d) between both groups (Fig. 4, lower panel).

DISCUSSION

The present results demonstrate a decreased ability of uterine muscle from eclamptic rats to respond to isoproterenol. This phenomenon, which was not observed with methoxamine, appeared to be secondary to receptor-mediated hydrolysis of arachidonic acid, and was not accompanied by changes in the expression and density of β-adrenergic receptors. In the present paper, we found that uteri from E rats, at a time when the isolated working tissue had a basal FA similar to that of C rats, was hyporesponsive to selective β-adrenoceptor stimulation by isoproterenol. The sensitivity of E tissue for the agonist, as derived from the concentration–effect relationship, decreased, while the maximal effect did not appear to be altered. This observation contrasts with data from receptor binding studies, in which neither the affinity (K_d) nor the density (B_{max}) of β-adrenoceptors was modified in the E and C groups. It is probable that in the alteration of the contractile effect of isoproterenol, other inotropic factors could be involved. The factor to take into account is the influence of inotropic action of PGE_2 in the contractile effect of isoproterenol. We show that the contractile response to isoproterenol in uteri from the E group was enhanced significantly by PLA_2 and cyclooxygenase inhibitors. Furthermore a subthreshold PGE_2 concentration reversed the effect of indomethacin. The fact that isoproterenol was able to trigger the release of PGE_2 by uteri from the E group suggests that PGE_2 could be mediating the hyporeactivity to isoproterenol observed in this experimental condition. The fact that verapamil affected the release of PGE_2 by isoproterenol suggests an alteration in calcium utilization in the E uteri that induces arachidonic acid hydrolysis after adrenoceptor occupancy, with a subsequent release of PGE_2.

We also demonstrated that PGE_2 triggers a positive inotropism, which was greater in uteri from the E group than from the C group. This increased ability of uteri from E rats to respond to PGE_2 is in agreement with the notion that the PGE_2 overload, which effect is opposite to that of isoproterenol, may subserve the hyporesponse of the uteri from the E group in response to β-adrenergic receptor activation.

Another factor involved in the alteration of the ino-

Table 4. Effects of β-adrenergic drugs and calcium blocker agents on release of PGE_2 by eclamptic (E) and control (C) uteri

Addition	PGE_2 released (pg/mg wet weight tissue)	
	C	E
None	4.41 ± 0.21	7.20 ± 0.31*
ISO	5.43 ± 0.33	14.60 ± 0.51†
ISO + PROP (10^{-7} M)	4.30 ± 0.20	8.22 ± 0.42
ISO + VERAP (10^{-5} M)	4.20 ± 0.30	6.60 ± 0.43

Values are means ± SEM of six experiments in each group, performed in duplicate. Uterine tissue was incubated in 2 mL of KRB in 5% CO_2 in O_2 at 37° with or without blockers [propranolol (PROP) or verapamil (VERAP)] for 90 min. Isoproterenol (ISO, 3×10^{-7} M) was added 3 min before total incubation time was over. A routine radioimmunoassay for PGE_2 was done.

* $P < 0.001$, C vs E (None).

† $P < 0.001$, E (None) vs ISO E.

Table 5. Effects of isoproterenol and PGE_2 on cAMP production by uteri from eclamptic (E) and control (C) rats

Addition	cAMP produced (pmol/mg wet wt tissue)	
	C	E
None	1.47 ± 0.12	2.81 ± 0.22*
ISO	3.58 ± 0.33†	3.01 ± 0.26
ISO + PROP	1.50 ± 0.14	2.11 ± 0.10
ISO + INDO	3.49 ± 0.40	2.90 ± 0.23
PGE_2	1.60 ± 0.10	5.10 ± 0.42‡
PGE_2 + PROP	1.31 ± 0.11	5.50 ± 0.44

Values are means ± SEM of six experiments performed in duplicate in each group. Uterine strips were incubated in KRB with 5% CO_2 in O_2 at 37° for 15 min with or without propranolol (PROP, 10^{-6} M) or indomethacin (INDO, 10^{-6} M) and then for 3 min more alone or with isoproterenol (3×10^{-7} M) or PGE_2 (10^{-7} M). Total incubation time was 30 min in all experimental conditions. A routine radioimmunoassay for cAMP was done.

* $P < 0.001$ vs C (None).

† $P < 0.001$ vs basal (None) C.

‡ $P < 0.005$ vs basal (None) E.

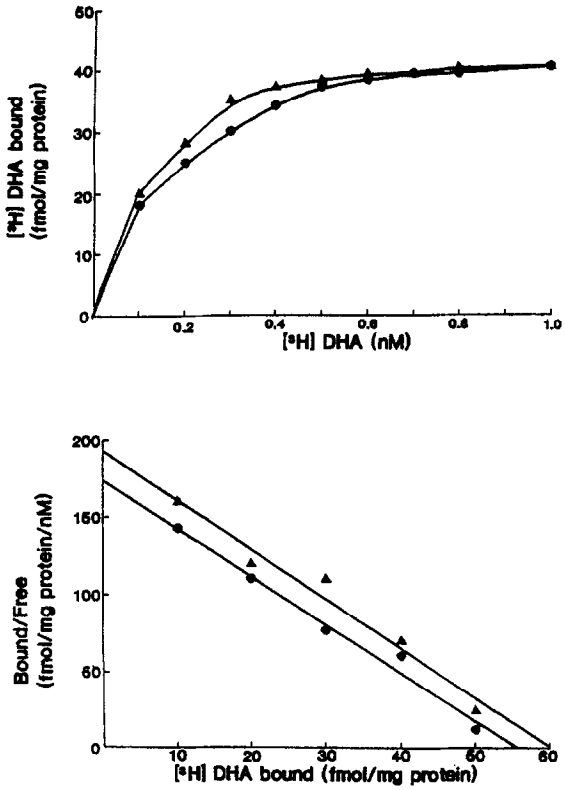

Fig. 4. [^{3}H]DHA binding to uterine membranes from control (C, ●—●) and eclamptic (E, ▲—▲) rats. Upper panel: saturation assays. Lower panel: Scatchard analysis. Binding parameters: E: B_{max}, 55 ± 4 fmol/mg protein; K_d, 0.33 ± 0.03 nM. C: B_{max}, 60 ± 5 fmol/mg protein; K_d, 0.35 ± 0.04 nM. These plots are representative of 5 other plots from experiments performed in duplicate.

tropic response of uteri from E rats to isoproterenol appears to be the decreased ability of the β-agonist to increase cAMP production, whereas E uteri are able to raise cAMP levels in response to PGE_2. These results could be explained by the fact that the PGE_2 overload in uteri from E rats induces a heterologous desensitization of uterine β-adrenoceptors, which could undergo phosphorylation [19]. By this mechanism, a modulation of the cAMP content of the rat myometrium with desensitization to isoproterenol by PGE_2, which does not ordinarily combine with this receptor but also activates the adenylate cyclase system, has been shown by others [20, 21]. However, cAMP does not have an exclusive role in mediating uterine relaxation by β-adrenergic agonists [20]; the exact role of cAMP in the modulation of contractile activity in the myometrium is poorly understood and remains controversial [22].

Differences in the reactivity of β-adrenoceptors in physiological and pathological conditions associated with generation of oxidative products of arachidonic acid have been described. Thus, in allogeneic pregnancy, the semiallogeneic fetus plays a distinctive immunological role producing, among other factors, PGE_2 that, in term, regulates the expression, coupling and signal transduction of uterine β-adrenergic receptors [4]. On the other hand, in diabetic conditions, the overload of thromboxane may modulate the β-adrenergic reactivity of the heart, potentiating the inotropic response of isoproterenol and exerting a negative feedback control to β-adrenoceptors [23].

In this paper, we suggested that the overload of PGE_2 may modulate the β-adrenergic reactivity of E rat uteri, diminishing the inotropic negative response, via direct interaction with PGE_2 receptors and exerting heterologous desensitization on β-adrenergic receptors. Regulation of uterine motility is one of the important factors for a successful pregnancy [24]. In this way, the β-adrenergic system is a potent inhibitor of uterine motility and could be involved in the maintenance of uterine quiescence during pregnancy. It is possible that the diminished responses to β-adrenergic stimulation described in this paper could be associated with an alteration of uterine vascular resistance and with an inadequate response of uterine muscle during labor [25].

Even though PGE_2 plays an important role as an immunomodulator during normal pregnancy [26], in the course of gestosis the great local release of this prostanoid could be masking the beneficial action of the β-adrenergic system on uterine contraction.

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