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EFFECT OF ERGOTAMINE ON THE VASOCONSTRICTIVE RESPONSES OF THE MAIN INTACT AND DENUDED OVINE UTERINE ARTERY TO 5-HT

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ABSTRACT

Because of the importance of blood flow from the mother to fetus, and the role of the main uterine artery to convey blood . The effect of ergotamine as a vasoconstrictor on the contractility of such artery was studied. Thus, light was shed on the importance of the lining epithelium in counter acting the effect of some vasoconstrictors and the role of EDRF (Endothelium Derived Releasing Factor) . The main uterine artery was isolated and removed without stretching, placed in a modified Krebs-Henseleit solution and oxygenated with carbogen . Some pieces were denuded and the others were kept intact ones. After equilibration, 5- hydroxytryptamine (5-HT) was added to the bath of all tissues and dose response curve (DRC) for 5-HT was constructed. Ergotamine was added in different concentrations; 10^{-6} , 10^{-7} and 10^{-8} to all tissues over 1 hour. Then DRC of 5-HT is constructed . Ergotamine diminished 52% of the contractile effect of 5-HT. The present work indicates that the endothelium of the main uterine artery in pregnant ewes near term play a role in keeping the contractile power of uterine artery less responsive to vasoconstrictors like ergotamine in pregnant ewes.

INTRODUCTION

Many ergot alkaloids appear to be partial agonists to 5-HT receptors)[1] . When concentration response curves for 5-HT is established in the presence of increasing concentrations of dihydroergotamine (0.1 -3 μmol/L) the maximal responses to 5-HT were progressively diminished and 10 μmol/L dihydroergotamine completely abolished the vasoconstrictor responses to 5-HT. The calculated parameters for antagonism by dihydroergotamine indicated that dihydroergotamine was 20 times more potent as antagonist towards the 5-HT receptor than towards the adrenergic ones [2] .

Recently, evidence has been provided for the importance of endothelium in the regulation of vascular smooth muscle tone [3,4]. Several vasoactive substances release the so called EDRF from endothelial cells by a receptor mediated process. This factor stimulates the formation of cGMP via activation of guanylate cyclase, thereby inducing relaxation of smooth muscle[5,6] .

More lately, EDRF has been identified as nitric oxide [7,8]. The vasoconstrictor effect of substances such as histamine, 5-HT, α-adrenoceptor agonists, angiotensin and peptides is enhanced on endothelium-denuded rat aorta[9-14] .

Removal of endothelium from isolated rabbit coronary arteries resulted in an increase in the contractile response to ergotamine [15]. The release of EDRF depends on the presnce of intact indothelium[12,14,16]. It has been found that dihydroergotamine did not change or induce small contractile response in the presence of intact epithelium [17] . While in endothelium-denuded aortic rings a pronounced contraction-dependent increase in tension was observed. The 5-HT receptors are being involved in the dihydroergotamine - induced vasoconstriction since this effect was inhibited by the 5-HT antagonist cyproheptadine .

The aim of the present study is to investigate the effect of ergotamine in different concentrations on 5-HT induced vasoconstriction in isolated uterine artery of pregnant ewes near term and role, if any, of the endothelium derived releasing factor.

MATERIALS AND METHODS

Adult pregnant mixed breed sheep near term were anaesthetized with pentobarbital and then exsanguinated. Pentobarbital was administered via the external left jugular vein. An incision in the abdomen was made and the uterus is exposed. The main uterine arteries were isolated and removed without stretching and placed in a modified krebs-Henseleit solution of the following composition : NaCl, 115.21 ; KCl, 4.70 ; $CaCl_2$, 1.8 ; $MgSO_4$, 1.16 ; KH_2PO_4, 1.18 ; $NaHCO_3$, 22.14 ; dextrose, 7.88. Disodium ethylenediamine tetra acetic acid (EDTA 0.03 mM) was added to suppress oxidation of amines. Kreb's solution was oxygenated with a mixture of oxygen carbon dioxide (95:5)[18]. Tissues were cut to small pieces almost 3mm long each. In some rings the endothelium was removed by gentle rubbing of the intimal surface with a saline-wetted cotton swab before the rings were hanged[19].

All tissues were hanged in organ bath under 1.0g tension and they were adjusted every 10 minutes for at least 90 minutes to allow equilibration before beginning of the experiment. Tensions developed by the tissues were measured isometrically by a transducer attached to a Grass Polygraph. After equilipration time 5-HT was added to all tissues. Dose response curve (DRC) was constructed by cumulative addition of the 5-HT in approximately one-half log increments[20] . After recording the maximum response of the highest dose of 5-HT (10^{-4} M) tissues were washed to allow them to get down to the base line of 1.0 g tension then from each of the two groups (intact and denuded) one

tissue was taken to represent time control. Ergotamine was added to all tissues, in different concentrations; 10^{-6}, 10^{-7} and 10^{-8} M; then tissues were allowed to adapt with ergotamine at least 1 hour and then the 5-HT dose response curve is constructed again to all tissues including the time controls. Addition of 5-HT was done at the peak of ergotamine contraction.

Statistical analysis was carried out according to Tallarida and Murray [21] using Student's "t" test to calculate the Mean ± SEM of the responses of different doses regarding the highest peak of 5-HT control as the 100% of contraction.

RESULTS

1) Response of intact uterine artery to 5-HT dose response curve and ergotamine :

As shown in Figure (1) the intact arterial rings treated with the different concentrations of ergotamine showed a significant decrease ($P<0.01$) in contractile response compared to control. The responses were 67.33±3.75, 48.0±2.51 and 76.33±3.28% for rings treated with ergotamine at 10^{-6}, 10^{-7} and 10^{-8} M respectively. There was a significant difference ($P<0.05$) between responses of 10^{-6} M and 10^{-7} and between 10^{-6} and 10^{-8} M.

2) Response of endothelium-denuded uterine artery to 5-HT dose response curve and ergotamine :

Figure (2) showed a significant decrease ($P<0.01$) in contractile responses to 53.66 ± 2.96, 58.66 ± 2.72 and 64.33± 2.60 for 10^{-6} M, 10^{-7} and 10^{-8} M respectively compared to control. The three concentrations didn't show any significance between each others.

3) Role of denudation in response to ergotamine :

Although there is a significant decrease ($P<0.05$) in the responses of the denuded rings to both concentrations of ergotamine 10^{-6} and 10^{-8} compared to the intact rings, the 10^{-7}M concentration showed an adverse picture since response of the denuded rings increased significantly ($P<0.05$) than the intact ones.

DISCUSSION

The present results indicate that when concentration response curve for 5-HT is established in the presence of increasing concentrations of ergotamine, the maximal vasocontractility responses of uterine artery to 5-HT was progressively diminished to 48% and this result coincides with those previously reported [1,2].

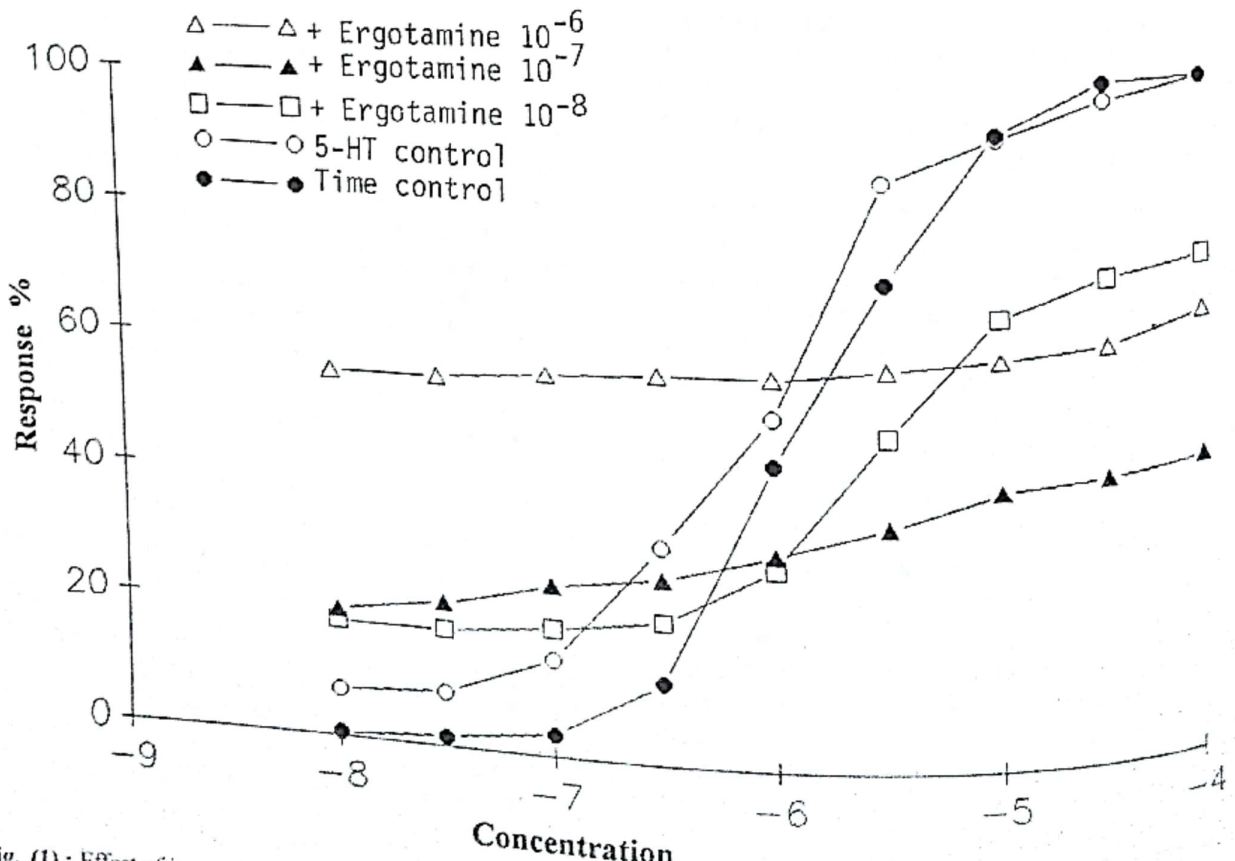

Fig. (1) : Effect of increasing concentrations of Ergotamine on the 5-HT induced contractions in an intact uterine artery of pregnant ewes near term. Concentration-dependent increases were obtained in the absence (Control and Time control) and the presence of increasing concentrations of Ergotamine. (Maximum response 100% -10^{-4}).

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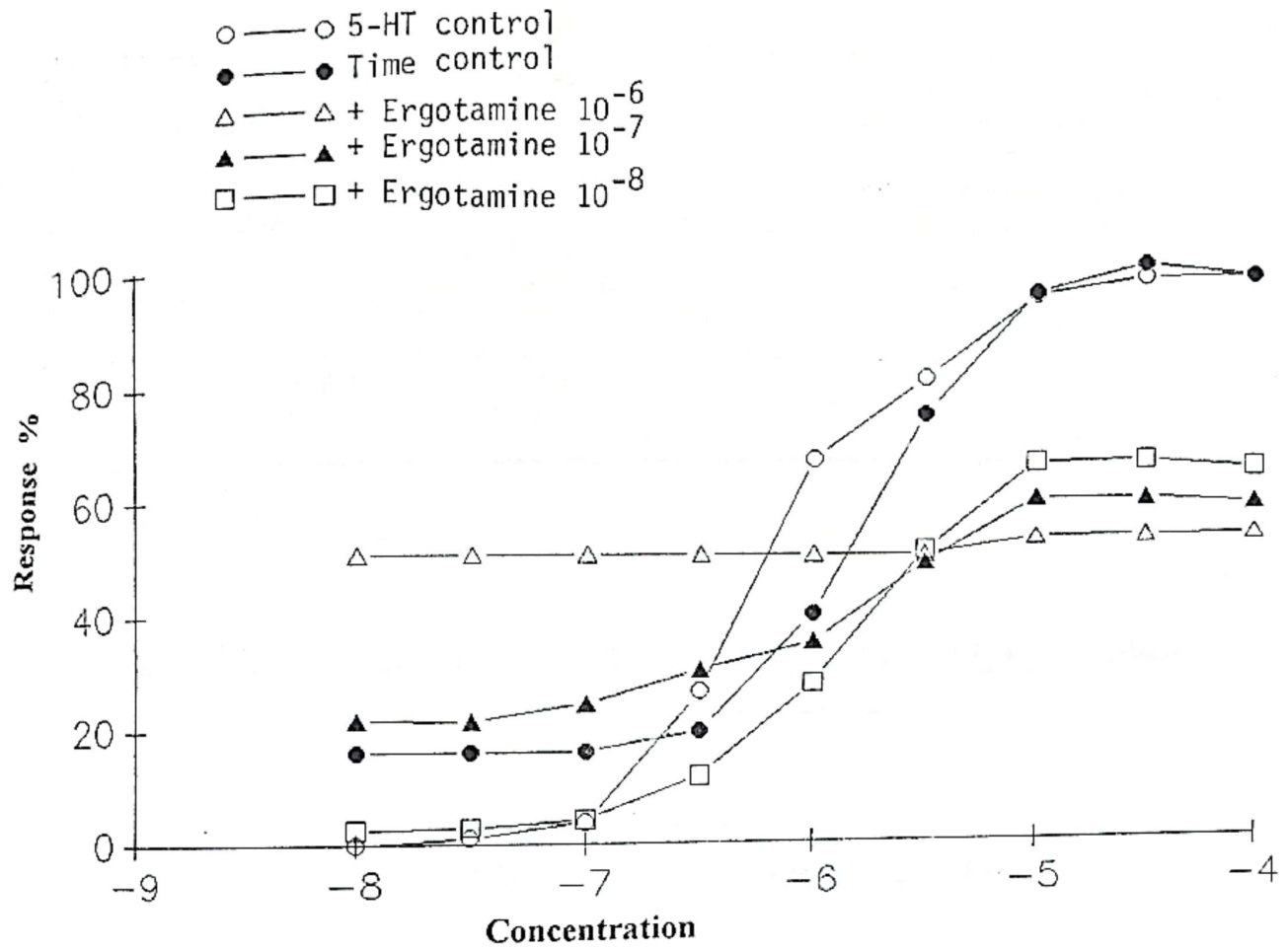

Fig. (2) : Effect of increasing concentrations of Ergotamine on the 5-HT induced contractions in denuded uterine artery of pregnant ewes near term. Concentration-dependent increases were obtained in the absence (Control and Time control) and the presence of increasing concentrations of Ergotamine. (Maxumum response 100% -10^{-4}) .

Since the removal of the endothelium from isolated rabbit coronary arteries results in an increase in contractile response to ergotamine [15]. Nevertheless, in the present study, ergotamine did not evoke different activity on denuded uterine arterial rings compared to intact rings this may allude to the fact that EDRF is not mediated by ergotamine in case of ovine uterine artery

In case of intact vessels the response of treated rings with 10^{-8} M ergotamine to 5-HT DRC was higher in the maximal resopnse than rings treated by 10^{-6} M and 10^{-7} M and this may agree with the results shown by Muller et al [2] who found that maximal response of 5-HT progressively diminished by dihydroergotamine in low doses while completely abolished vasoconstrictive responses to 5-HT when used in large doses.

In endothelium-denuded arterial rings 5-HT DRC was lower in ergotamine treated rings than those of intact ones and this is quiet different from the work done before [10-14]. They found that the vasoconstrictor effect of histamine, 5-HT, α-receptors agonists, angiotensin and peptides is enhanced in endothelium-denuded rat aorta.

The present work indicates that the endothelium of the main uterine artery in pregnant ewes near term plays a role in keeping the contractile power of uterine artery less responsive to some vasoconstrictors drugs like ergotamine.

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التأثير الانقباضى للارجوتامين على الشريان الرئيسى للرحم فى النعاج الحوامل فى وجود الغشاء المبطن له من عدمه بعد معالجته بالسيروتونين .

جمال عبد الدايم على
قسم التكاثر والتلقيح الصناعى -المركز القومى للبحوث-الدقى - الجيزة

نظرا لأهمية سريان الدم من الأم الى الجنين خلال الشريان الرئيسى للرحم فقد وضعت هذه الدراسه لمحاولة معرفة تأثير مادة الأرجوتامين كمادة قابضة للأوعيةالدمويه علي هذا الشريان الحيوى . ولالقاء الضوء على أهمية وجود الغشاء المبطن من تلافى التأثير الانقباضى لبعض الأدويه من خلال خروج عامل الارتخاء من الأندوثيليم (EDRF).

تم استخدام قطع من الشريان الرئيسى للرحم المعزولة من النعاج الحوامل فى نهاية الحمل وتم معالجة جزء من هذه الحلقات المأخوذه بقطعة قطن مبللة بمحلول ملحى لازالة الغشاء المبطن . تم تعليق المجموعتين التى لم تعامل والمجموعة التى تم ازالة غشاءها وذلك لفترة كافية حوالى ٩٠ دقيقه ثم اضافة محلول السيروتونين (5-HT) والحصول على منحنى تجميعى حتى أعلى تركيز (10^{-4} M) ثم تم غسل الحلقات وعند عودتها الى الخط القاعدى للشد المحسوب له (١ جرام) تم اضافة الأرجوتامين لكل الحلقات ماعدا الحلقه الضابطه وكانت التركيزات هى 10^{-6} ، 10^{-7} ، 10^{-8} عيار .

اشارت النتائج فى هذه الدراسه الى أن كل الحلقات قد تأثرت بالارجوتامين بدرجات متفاوته وقلت نسبة الانقباض الى أن وصلت الى حوالى ٤٨ ٪ من الانقباض الرئيسى بالسيروتونين (5-HT) وبتأثير معنوى . هذا ولم يكن هناك اختلاف معنوى بين التركيزات المختلفة فى حالة الحلقات منزوعة الغشاء .

وأخيرا قد يتضح من هذه التجربه أن الغشاء المبطن للشريان الرئيسى للرحم فى النعاج الحوامل قد يلعب دورا فى حفظ التأثير الانقباضى للشريان بالايتأثر ببعض المواد القابضه ومنها الارجوتامين مما يحافظ على ألا تتأثر كمية الدماء الواصله للجنين .