

## INHIBITORY EFFECT OF SPIRONOLACTONE ON THE CONTRACTIONS OF THE RABBIT UTERINE HORN AND THE HUMAN MYOMETRIAL STRIP.

BEKIR COKSEVIM\* AND MEHMET TAYYAR\*\*

\**Department of Physiology and*

\*\**Department of Obstetrics and Gynecology,  
University of Erziyes, Faculty of Medicine,  
Kayseri, Turkey*

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**Abstract :** The spontaneous contractions of the rabbit uterine horns and the human myometrial strips were stimulated by oxytocin and buserelin acetate in isolated preparations. Spironolactone application to these models produced inhibitory effects on the contractions. It is concluded that spironolactone has inhibitory effect on the rabbit uterine horn and the human myometrial strip contractions.

**Key words :** spironolactone      rabbit uterine horn      human myometrial strip

### INTRODUCTION

Spironolactone (SP) is an aldosterone antagonist that is used in the treatment of congestive heart failure, primary aldosteronism, hepatic ascites, essential hypertension, hirsutism acne, precocious puberty, and premenstrual tension (1,2,3,4,5,6).

In our unpublished data on rats, we observed inhibitory effect of SP on the ileum, trachea and uterine (all of them have smooth muscle) spontaneous contractions. Up to date we did not coincide a manuscript about the effects of SP on the uterus. Therefore, we planned to study the effect of SP on the human myometrium and the rabbit uterine horn.

We used oxytocin (Oxy) and a gonadotropin releasing hormone (GnRH) agonist buserelin acetate (BA) to stimulate spontaneous contractions. The stimulatory effect of GnRH agonist leuprolide acetate on the human myometrium firstly reported by Kendall et al (7). We studied GnRH agonist BA on the human myometrial strip and the rabbit uterine horn motilities and observed the stimulatory effect of BA on the spontaneous uterine contractions (8). Because of this new knowledge we decided to study SP on the Oxy and BA stimulated uterine contractions.

### METHODS

The study was realised at the Erziyes University Physiological Experimental Laboratory. Female New Zealand white rabbits were used for the study and their weights were 2500 g to 3000 g. Intraperitoneal thiopental 30 mg/kg in dose was used to get general anaesthesia. The abdomen of the rabbits were opened through a ventral midline incision. The uterine horns were excised and used for isolated preparations. The human myometrial strips were obtained from the tissues excised at hysterectomy from the patients with dysfunctional uterine bleeding.

The human myometrial strips and the rabbit uterine horns were suspended in the organ bath containing 15 cc of Lock-Ringer's solution. The temperature of this solution was kept 37°C. It was aired by 95% oxygen and its pH was 7.4. One end of the uterine horn and the myometrial strip were applied to the transducer. The tension of 5 g was applied to the human myometrial strip and 1 g tension was applied to the rabbit uterine horn.

Control and experimental motility traces were recorded by force displacement transducer (TB 611 T Nihon Kohden) by using polygraphic system (RM 6000 Nihon Kohden). Amplitude, duration and frequency of

\*\*Corresponding Author : P.K. 316, 38002 Kayseri, TURKEY

the contractions were observed and the samples of the traces were recorded during application of the agents (Oxy, BA, ritodrine hydrochloride (Rit), SP).

Oxy (Synpitan, Deva Co., Istanbul, Turkey) was used in dose  $0.5 \times 10^{-3}$  IU/ml to  $1.0 \times 10^{-2}$  IU/ml to stimulate contractions. Also, GnRH agonist BA (Suprefact, Hoechst, AG, Frankfurt, Germany) was used in doses  $0.105 \times 10^{-2}$  mg/ml to  $1.05 \times 10^{-2}$  mg/ml to stimulate contractions. SP (Potassium Canrenoate-Sanofi Chimie Co., France) was used  $0.1 \times 10^{-3}$  mg/ml to  $0.2 \times 10^{-3}$  mg/ml doses to inhibit the contractions. Also, well known tocolytic agent Rit (Prepar, Eczacibasi, Co., Istanbul, Turkey) was used  $1.25 \times 10^{-3}$  mg/ml to  $2.5 \times 10^{-3}$  mg/ml to compare the inhibitory effect of SP.

The traces were analysed according to their amplitude, tension, and inhibition percentage. Statistical analysis were performed using Student-t test.

## RESULTS

The inhibitory effects of SP on the stimulated

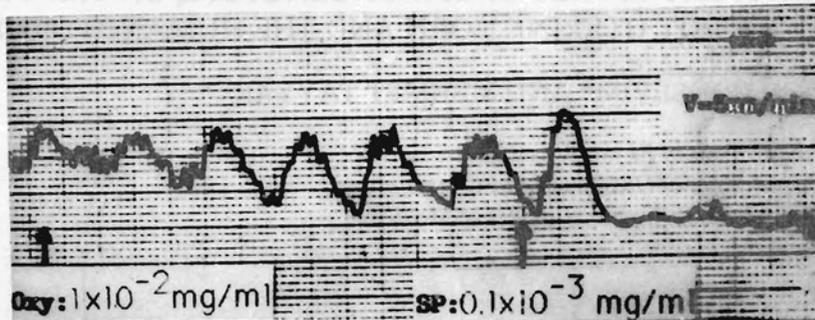


Fig. 1 : Shows the inhibitory effect of SP on the Oxy stimulated human uterine myometrial strip.

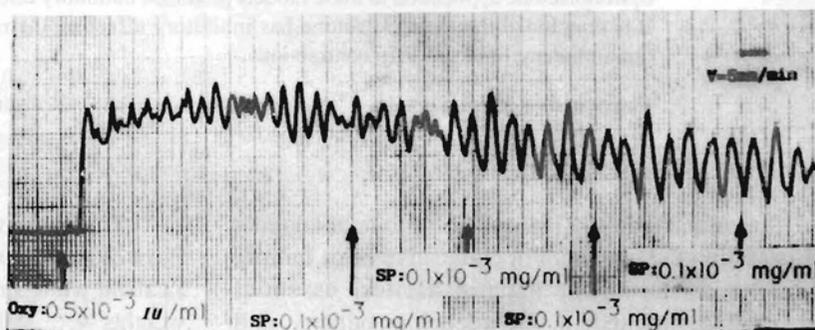


Fig. 2 : Shows the inhibitory effect of SP on the Oxy stimulated rabbit uterine horn.

spontaneous contractions are presented in Table I. Fig. 1 and 2 shows the inhibitory effect of SP on the contractions of human myometrial strip and rabbit uterine horn contractions which were stimulated by Oxy. Fig. 3 and 4 shows the inhibitory effect of SP on the contractions of human myometrial strip and rabbit uterine

TABLE I : The inhibitory effect of SP on the human myometrium strip and the rabbit uterine horn.

The name of the preparation	Amplitude and Tension	Induction (mm)		Inhibition (mm) X ± SD SP	Inhibition (%)
		X ± SD Oxy	X ± SD BA		
Human Myometrial Strip (n:10)	Tension (mm)	8.48 ± 1.67	—	0.05 ± 0.01*	100.0
	Amplitude (mm)	21.00 ± 1.84	17.80 ± 8.15	5.20 ± 3.80* 4.70 ± 2.27*	64.0 77.6
Rabbit Uterine Horn (n:10)	Tension (mm)	19.90 ± 1.64	—	2.25 ± 0.82*	88.6
	Amplitude (mm)	27.40 ± 1.77	5.16 ± 3.9	2.50 ± 0.50* 3.20 ± 0.10* 7.60 ± 0.90*	51.5 88.3 74.2

\*Statistical comparison showed statistically significant difference when compared to the induction levels ((P<0.05).

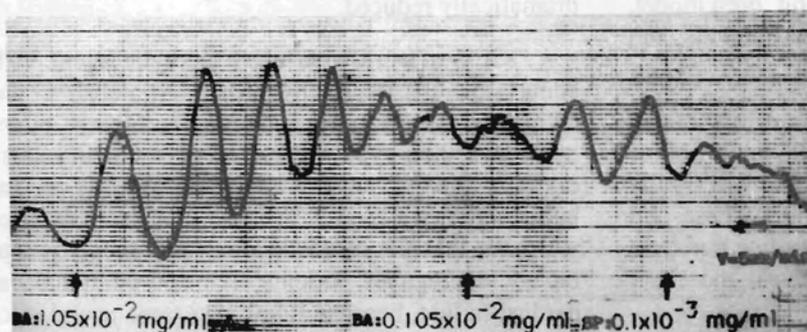


Fig. 3 : Shows the inhibitory effect of SP on the BA stimulated human myometrial strip.

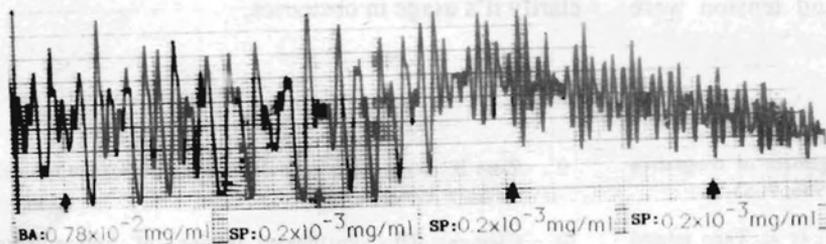


Fig. 4 : Shows the inhibitory effect of SP on the BA stimulated rabbit uterine horn.

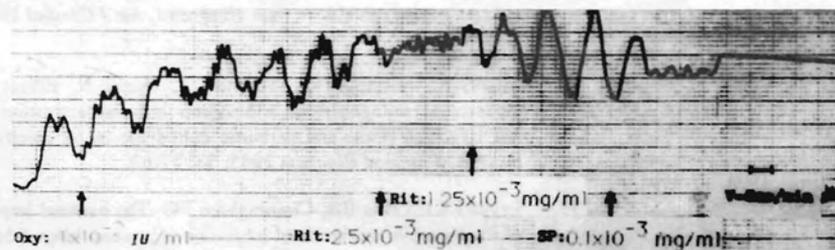


Fig. 5 : Shows the inhibitory effect of Rit and SP on the Oxy stimulated human myometrial strip.

horn contractions which were stimulated by BA.

When the human myometrial strip contractions were stimulated by Oxy the tension was inhibited 100% by using SP. Whereas BA stimulated experiments showed 64% inhibition. Statistical analysis revealed that tension values got by inducing and inhibiting have significant differences ( $P < 0.05$ ). Amplitude levels shows 77.6% inhibition when SP applied to the Oxy stimulated contractions of the human myometrial strip. But, BA induced contractions showed 44.5% amplitude

inhibition. Therefore, amplitude inhibition values of SP showed statistically significant ( $P < 0.05$ ) difference between Oxy and BA used preparations.

When the rabbit uterine horn contractions were stimulated by Oxy the tension was inhibited 88.6% by using SP. Whereas BA stimulated experiments showed 51.5% inhibition. Statistical analyses revealed that tension values got by inducing and inhibiting have significant differences ( $P < 0.05$ ). Amplitude levels showed 88.3% inhibition when SP applied to the Oxy stimulated contractions of the rabbit uterine horn. But, BA induced contractions showed 74.2% amplitude inhibition. Therefore, amplitude inhibition values of SP showed statistically significant ( $P < 0.05$ ) difference between Oxy and BA used preparations.

Also, we investigated Rit and SP on the Oxy stimulated contractions of the human myometrial strip in order to compare their inhibitory effects (Fig. 5).

## DISCUSSION

In our unpublished data we used SP on the trachea, ileum, and uterus of the rat as isolated preparations, and we got inhibitory effects on their spontaneous activities. Even we concluded that the SP could be used as tocolytic agent. To get more support were planned the present study.

According to our data SP has inhibitory effect on the BA and Oxy stimulated spontaneous contractions of the rabbit horn and the human myometrial strip.

The tension was less reduced in the rabbit horn model. This is probably due to different contractions and dispersion of the receptors in the rabbit.

Probable pathways of inhibitory effect of SP are; (a) effect on the receptor level, (b) inhibition of adenylyl cyclase activity, (c) slow calcium channels similar to that calcium blockers, (d) inhibiting ATPase and carbonic anhydrase, (e) modifying electrolyte transport (9,10,11,12). Further analyses shall reveal the exact pathway of inhibitory effect of SP.

To test the inhibitory effect of SP on the contractions Rit was applied to the preparations and cumulative doses of Rit produced amplitude and tension increment. At that time SP was applied to the preparation. Then, the amplitude and tension were

dramatically reduced.

Rit is a worldwide used tocolytic agent. It has some side effects (tachycardia, hypotension, chest tightness or actual pain, pulmonary edema, hyperglycemia, hypokalemia, lactic and ketoacidosis, emesis, headaches, tremulousness, fever and hallucinations) (13,14). Because of these side effects we think that SP could be used as a tocolytic agent on some pregnant patients like cor pulmonale and cardiac failure, because it has also some useful effects (positive inotropic effect, potassium sparing effect (15,16).

In conclusion, SP has efficient inhibitory effect on the uterus contractions. Further clinical analysis shall clarify its usage in obstetrics.

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