

# MODULATION OF 5-HYDROXYTRYPTAMINE-EVOKED RESPONSES OF THE ISOLATED RAT UTERUS BY IMIDAZOLE, A PHOSPHODIESTERASE STIMULATOR

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**Summary :** Imidazole, a phosphodiesterase stimulator potentiated the responses of rat uterus to 5-HT, without increasing the maximal response. Aminophylline, papaverine and diazoxide significantly inhibited the responses to 5-HT including the maximal response. Imidazole did not affect the inhibitory effect of aminophylline, papaverine and diazoxide. The effect of imidazole on myometrium may be due to its direct effect on membrane permeability resulting in an increased influx of calcium. Phosphodiesterase stimulation if at all seems to play only a minor role.

**Key words :** rat uterus      inhibitors      imidazole      5-hydroxytryptamine      PDE

## INTRODUCTION

The profound stimulatory effect of imidazole on pregnant rabbit uterus is explained on the basis of its phosphodiesterase (PDE) stimulant property (2). But Polacek and Daniel (4) failed to correlate the onset of uterine contraction induced with imidazole to the decreased levels of cyclic AMP. Recent reports from our own laboratory also did not implicate PDE-cyclic AMP system in the effect of imidazole on uterine motility (5,6) when uterine stimulants other than 5-hydroxytryptamine, (5-HT) were used. The present study was designed to elucidate further the mechanism involved in the action of imidazole on the myometrium, when 5-HT was used as uterine stimulant.

## MATERIAL AND METHODS

Oestrus was induced in female rat with oestradiol dipropionate (200  $\mu$ g, sc), 15 hr prior to the experiment. A piece of the cervical end of the uterine horn was removed and suspended in an organ bath of 10 ml capacity, containing aerated de Jalon solution (Composition, g/L: NaCl 9.0, KCl 0.41,  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.06, glucose 0.5,  $\text{NaHCO}_3$  1.0) at 30°C. The contractions were recorded isotonically on a smoked kymograph using a frontal rwiting lever (magnification, X6 tension on the tissue was 0.25 g). After stabilisation of the tissue for 30 min a cumulative dose-response curve (CDRC) for 5-HT was recorded, each dose being allowed to act for 60 sec.

The preparation was then exposed to de Jalon solution containing imidazole ( $3.67 \times 10^{-3}\text{M}$ , pH adjusted to 7.2 with HCl) aminophylline ( $5.7 \times 10^{-4}\text{M}$ ) papaverine ( $9.3 \times 10^{-6}\text{M}$ ) or diazoxide ( $1.08 \times 10^{-3}\text{M}$ ) for 30 min and then another CDRC was recorded. The preparation was washed repeatedly for 90 min and CDRC was recorded. Moreover in the case of PDE inhibitors (aminophylline, papaverine, diazoxide) the tissue was further exposed to the combination of respective PDE inhibitor used and imidazole for 30 min and a CDRC of 5-HT was recorded.

In addition to these treatment groups a control group was constituted in which CDRC was recorded initially, after 30 min and 150 min. Moreover time corrected control values were employed to analyse the effect of PDE regulators treatment. Each treatment and control group consisted of replication of 5 experiments. Student 't' test was used for statistical analysis of the data.

## RESULTS

5-HT evoked control uterine responses decreased when recorded after 30 min and 150 min time interval. The decrease was statistically significant only at few dose levels. Imidazole ( $3.67 \times 10^{-3}\text{M}$ ) produced transient contracture of myometrium which subsided in 5-6 min. Moreover, imidazole increased the responses evoked by 5-HT but there was no alteration in the maximal response though the CDRC was shifted to left. Aminophylline ( $5.7 \times 10^{-4}\text{M}$ ), papavarine ( $9.3 \times 10^{-6}\text{M}$ ) and diazoxide ( $1.08 \times 10^{-3}\text{M}$ ) significantly decreased the responses of 5-HT and shifted the CDRC towards the right, with a marked decrease in maximal response. The antagonism was reversible in all cases and CDRC returned almost to the control curve after the tissue was repeatedly washed for 90 min. Imidazole treatment did not significantl ayter the inhibitory effect of aminophylline, papaverine and diazoxide.

TABLE 1: Effect of PDE regulators on 5-HT-evoked responses of isolated rat uterus.  
(Values are mean  $\pm$  S.E. from 5 experiments)

Treatment	Contraction (% of maximal) due to 5-HT (M)					
	1.2 X 10 <sup>-9</sup>	6.3 X 10 <sup>-9</sup>	3.16 X 10 <sup>-8</sup>	1.5 X 10 <sup>-7</sup>	7.9. X 10 <sup>-7</sup>	3.9 X 10 <sup>-6</sup>
Nil (Thirty min time corrected control)	12.81 $\pm$ 5.40	58.23 $\pm$ 12.56	72.52 $\pm$ 5.48	84.02 $\pm$ 3.12	89.41 $\pm$ 4.82	93.09 $\pm$ 6.60
AMINOPHYLLINE (5.7 X 10 <sup>-4</sup> M)	1.51 $\pm$ 1.10	12.91* $\pm$ 5.07	26.82* $\pm$ 9.03	30.98** $\pm$ 9.50	35.81* $\pm$ 10.78	39.82* $\pm$ 10.30
DIAZOXIDE (1.08 X 10 <sup>-3</sup> M)	1.66 $\pm$ 1.66	11.52* $\pm$ 5.58	22.69** $\pm$ 8.43	29.87** $\pm$ 9.19	38.75** $\pm$ 9.16	48.96** $\pm$ 8.43
PAPAVERINE (9.30 X 10 <sup>-6</sup> M)	0.0* $\pm$ 0.0	2.51** $\pm$ 1.08	17.98** $\pm$ 2.70	28.93** $\pm$ 6.56	38.76** $\pm$ 9.29	43.87** $\pm$ 8.72
IMIDAZOLE (3.67 X 10 <sup>-3</sup> M, pH adjusted to 7.2 with HCl)	49.66* $\pm$ 15.22	70.37* $\pm$ 12.20	85.58* $\pm$ 9.39	94.81* $\pm$ 4.9	99.75 $\pm$ 4.18	99.81 $\pm$ 0.44

Value significantly differs from control ( \*P<0.05)  
(\*\*P<0.01)

## DISCUSSION

The present study demonstrated a non-competitive antagonism between PDE inhibitors (aminophylline, papaverine, diazoxide) and 5-HT. Imidazole produced a transient contracture of the myometrium and significantly increased the responses evoked by 5-HT. Imidazole is known to activate PDE and consequently decrease intracellular cyclic AMP levels (2, 3). In addition it may produce a non-specific activation of contractile machinery through the mobilisation of calcium (1). The observed effect of imidazole appears to be due to change in membrane permeability and increased influx of calcium because it failed to reverse the inhibitory effect of aminophylline, papaverine and diazoxide, the well known PDE inhibitors. Moreover, the transient contracture of myometrium with imidazole is also more likely to be the result of depolarisation of cell membrane and increased influx of calcium since Polacek and Daniel (4) did not observe a correlation between

such contracture and the decrease in cyclic AMP levels. Thus modulation of 5-HT evoked uterine responses by imidazole seems to be due to increased mobilization of calcium rather than to its PDE stimulant property. It further supports our earlier inferences on the mechanism of action of imidazole on uterine motility (5,6) obtained with other agonists.

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