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Involvement of α-adrenoceptors in myometrial responses in the pro-oestral rat

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1 Myometrial responses to different agents acting on adrenoceptors were examined *in vivo* in the pro-oestrous rat. Changes in spontaneous uterine mechanical activity were recorded isometrically and evaluated in terms of amplitude and duration of uterine contractions.

2 Phenylephrine (10 $\mu g\,kg^{-1}$) markedly increased the amplitude and duration of contractions and 40 $\mu g\,kg^{-1}$ gave rise to tetanic contractions.

3 Administration of either nicergoline (400 $\mu g\,kg^{-1}$) or phentolamine (1000 $\mu g\,kg^{-1}$) to phenylephrine-primed rat uterus reduced the strength of contractions and phentolamine abolished the phenylephrine-induced uterine contracture.

4 Following blockade of α_2-adrenoceptors by yohimbine (1000 $\mu g\,kg^{-1}$) and β-adrenoceptors by propranolol (2400 $\mu g\,kg^{-1}$), a single injection of phenylephrine (100 $\mu g\,kg^{-1}$) increased the amplitude of uterine contractions by 30%.

5 Noradrenaline reduced the amplitude of contractions and caused elevation of the baseline level. The response of myometrium to the combination of both propranolol and noradrenaline was the establishment of uterine contracture with subsequent increase of the duration of contractions.

6 These results clearly demonstrate the involvement of α-adrenoceptors in the myometrial activity of the rat *in vivo* during pro-oestrus.

Introduction

Uterus, like many other smooth muscle tissues, shows autonomous myogenic activity which is dependent on calcium (Ca^{2+}) and adenosine 3′:5′-cyclic monophosphate (cyclic AMP) acting as synarchic messengers (Rasmussen, 1981). In uterine muscle relaxation is linked to a rise in cyclic AMP, while contraction is linked to Ca^{2+} elevation (Fain, 1984).

It is well known that catecholamines modulate uterine motility through stimulation of α-excitatory and β-inhibitory adrenoceptors. The degree of α- and β-adrenergic responsiveness is regulated by sex steroid hormones (Abdel-Aziz & Bakry, 1973; Krall *et al.*, 1978). Thus, the endocrine state of the uterus is of importance for the fluctuation of the adrenoceptor content in the uterine muscle (Digges, 1982). The β-adrenoceptor population can be divided into two subgroups, the β_1 and β_2. In the rat uterus, β-adrenoceptors are mainly of the β_2- type (Lands *et al.*, 1967; Borda *et al.*, 1979; Johansson *et al.*, 1980). Krall *et al.* (1978) noted an increased number of β-receptors in rat myometrium during pro-oestrus, when the concentration of 17-β-oestradiol is highest (Nequin *et al.*, 1979). α-Adrenoceptors can be differentiated into α_1- and α_2-subtypes (Wikberg, 1979) eliciting different responses (Garcia-Sainz *et al.*, 1980; Molinoff, 1984). In the past the existence of excitatory α-adrenoceptors in the myometrium has been denied (Rudzik & Miller, 1962; Levy & Tozzi, 1963). More recently their presence in the uterine muscle has been accepted (Rubio *et al.*, 1984; Estañ *et al.*, 1985), but in contrast to the β-adrenoceptors, myometrial content of α-adrenoceptors was not significantly elevated in the pro-oestrous rat (Krall *et al.*, 1978).

While there are numerous publications describing the effects of adrenoceptor agonists and antagonists on smooth muscle, few if any reports are available concerning their action on the pro-oestral rat uterus. In a recent study, we compared the myometrial responses of two adrenoceptor antagonists with those of noradrenaline and phentolamine in the rat during pro-oestrus (Acritopoulou-Fourcroy *et al.*, 1984). In the current investigation, on the pro-oestrous rat, we aimed to allow the expression *in vivo* of the α-myometrial adrenoceptors in order to determine their involvement in myometrial activity. Consequently, we have studied the effects of the following agents acting

on adrenoceptors: phenylephrine (PE), an α_1-adrenoceptor agonist; noradrenaline (NA), α- and β-adrenoceptor agonist; nicergoline (NI), an α_1-adrenoceptor antagonist; yohimbine (Yoh), an antagonist of α_2-adrenoceptors; phentolamine (Phent), a non-specific α-adrenoceptor blocking agent; propranolol (Prop), a non-specific β-adrenoceptor blocking agent.

Methods

Animal preparation

Adult female Wistar rats weighing 180–260 g were used on the day of pro-oestrus. The stage of the oestrous cycle was monitored by means of vaginal smears. Following anaesthesia with sodium pentobarbitone (Nembutal, 40 mg kg^{-1}, i.p., Abbot) the abdomen was opened by a midline incision and the rat was prepared for isometric recording of the mechanical activity of the uterine muscle, maintained *in situ*, as follows. The anterior end of one uterine horn was linked with an isometric strain gauge by means of a cotton thread passed near the oviduct. The gauge was connected to a transducer coupled to a polygraph (ECEM). The uterine horn was tied firmly with a second cotton thread passed towards the cervix to a metal rod held rigidly. While manipulating the reproductive tract care was taken to minimize its stretching. Throughout the experiment, the rat was maintained on a heated plate at 37°C and Tyrode solution (37°C) was dripped down the outside of the uterine horn to keep it moist.

Recording and measurement of the spontaneous uterine contractility

All experiments were carried out in the afternoon on the day of pro-oestrus, for we noted that uterine contractions started only late in the morning of pro-oestrus, when a precipitous fall in oestradiol concentration occurs (Nequin *et al.*, 1978). Following stabilization of the uterine activity, the variations of the spontaneous uterine contractions were recorded under saline administration via the femoral vein; this 'control recording' allowed us to evaluate the effect of the agents used on uterine activity. Following withdrawal of the agents acting on adrenoceptor a second recording under saline administration was carried out in order to have a 'reference' of the fluctuations in myometrial activity. The 'control recording' period as well as that following administration of each concentration of the tested compounds was of 30 min.

Variations in myometrial activity were evaluated in terms of amplitude and duration. We measured the maximum amplitude in mm of each uterine contraction of the 'control recording' period and a value of 100% was arbitrarily attributed to the control mean amplitude. The duration of contractions corresponds to the time (in s) between two successive relaxations of the uterine muscle. Both the mean amplitude and duration of the uterine contractions recorded following the administration of each dose of drug(s) were then compared with the corresponding mean of the 'control recording'.

Drugs

The compounds used in this study were: phenylephrine hydrochloride (gift: Faure-Annonay); noradrenaline (Levophed, Winthrop Labs); nicergoline (Sermion, gift: Specia Labs); yohimbine hydrochloride (Roussell UCLAF); phentolamine (Regitine, Lab Ciba Geigy); propranolol (Alvocardyl, ICI Pharma). With the exception of nicergoline and phenylephrine which were dissolved in sterile distilled water, appropriate dilutions of the drugs in sterile saline (0.9% w/v NaCl) were prepared immediately before use. They were all administered via the femoral vein, the adrenoceptor agonists, PE and NA, being infused in a volume of 5 ml saline (except PE in Table 2, group 3), while the antagonists (NI, yoh, Phent and Prop) were injected in a volume of 0.25 to 0.50 ml saline. Doses are expressed as $\mu g\ kg^{-1}$ body weight and indicate the successive amounts of drug(s) received by experimental animals at time intervals of 30 min. Drug dosage selection was based on our preliminary observations and on concentrations used by other research workers.

Statistics

All data, expressed as mean ± s.e.mean of at least seven values, are presented in Tables 1 and 2. Wilcoxon non-parametric statistics and in some cases Student's t test as well were used to compare significance of differences between means.

Results

Effects of phenylephrine, nicergoline and phentolamine administered alone or in combination

The results are presented in Table 1. Infusion of PE (at the rate of 10 $\mu g\ kg^{-1}$ during 30 min), a specific agonist at α_1-adrenoceptors, produced a mean increase of 25% in the amplitude of uterine contractions. Moreover, sustained uterine contracture of a tetanic type was recorded in 6 out of the 14 PE-treated rats which resulted in a significant increase ($P < 0.001$) of the mean duration of uterine contractions (see Table 1; group 1). As the infusion rate of PE was increased to 40 $\mu g\ kg^{-1}$, the uterine contracture, already noted in

Table 1 Effect of phenylephrine (PE), nicergoline (NI) and phentolamine (Phent) on amplitude and duration of uterine contractions in the pro-oestrous rat

Group of rats	*Agents used and dose* ($\mu g\,kg^{-1}$)	*No of rats* (*(n)*)	*Amplitude of contractions* (%) *range*	*Mean ± s.e.*	P*	*Duration of contractions* (s) *Range*	*Mean ± s.e.*	P*
1†	C: Saline	14	73–122	100 ± 5.1	—	44–79	65 ± 5.1	—
	PE 10	14	90–173	125 ± 9.9	<0.01	55–149	87 ± 12	<0.001
	PE 40	14	62–181	106 ± 14	NS	40–181	104 ± 23	<0.001
	[a]NI 400	7	52–122	66 ± 3.6	<0.001	36–232	123 ± 43	<0.001
	Saline	7	61–156	109 ± 16	NS	71–289	130 ± 50	<0.001
	[b]Phent 1000	7	24–99	63 ± 5.9	<0.001	34–82	63 ± 4.0	NS
	Saline	7	50–130	92 ± 8.5	NS	46–98	67 ± 6.5	NS
2	C: Saline	8	71–124	100 ± 8.0	—	33–54	42 ± 2.0	—
	NI 400	8	67–95	88 ± 7.1	NS	35–52	41–1.1	NS
	Saline	7	75–107	96 ± 7.6	NS	30–51	43 ± 2.2	NS
3	C: Saline	9	70–123	100 ± 5.6	—	38–84	56 ± 1.8	—
	Phent 1000	9	32–71	59 ± 4.3	<0.001	46–82	60 ± 2.0	<0.025
	Saline	8	58–104	85 ± 4.9	NS	35–93	57 ± 3.0	NS

C = control; NS = non-significant. Animals involved in the same group after saline were administered the drug(s) listed successively at intervals of 30 min.
*P values were obtained using Wilcoxon non-parametric statistics. †All 14 rats of the group were given successively: Saline; PE 10; PE 40; then, in subgroup (a) rats received NI 400 and saline while those in (b) received Phent 1000 and saline.

some animals at $10\,\mu g\,kg^{-1}$, was generalized and accentuated; amplitude was reduced nearly to its pre-drug (C: Saline) level.

Blockade of the α_1-adrenoceptors by NI did not significantly reduce the mean amplitude of uterine contraction (Table 1; group 2).

A single i.v. injection of NI following activation of the α_1-myometrial adrenoceptors by PE reduced abruptly the amplitude of uterine contractions (Figure 1), the overall NI inhibitory effect being 34% ($P<0.001$; group 1a). NI failed to abolish the PE-induced uterine contracture; consequently, the mean duration of spontaneous contraction was virtually doubled (65.0 ± 5.1 vs 123.0 ± 43.0 s).

Phentolamine when administered alone ($1000\,\mu g\,kg^{-1}$) induced an overall 40% fall ($P<0.001$) of the amplitude (Figure 2) and an increase of the duration of uterine contraction ($P<0.025$). When Phent was given after PE infusion, at the rate of $40\,\mu g\,kg^{-1}$ during 30 min, the myorelaxant effect of the former was more pronounced than previously and resulted in a 75% inhibition of the strength of uterine contractions within the first 10 min of its administration. Thereafter the uterine relaxation regressed rapidly and amplitude almost reached the control pre-drug value (95% vs 100%) at the end of the 30 min recording (Figure 2). Moreover, Phent abolished the uterine contracture induced by PE.

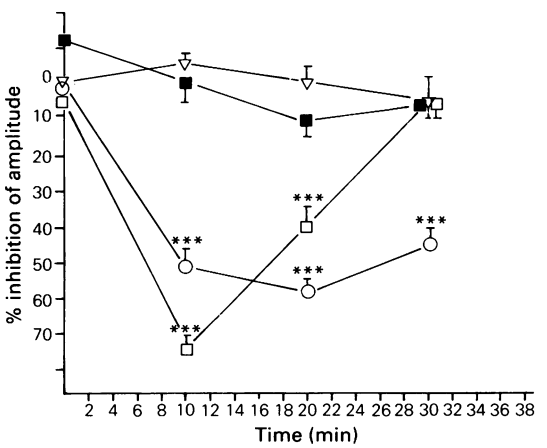

Figure 1 Inhibition (%) of amplitude of spontaneous uterine contraction in response to drug treatment in the pro-oestrous rat; each point represents the mean of 7 values; vertical lines show s.e.mean. Control (▽); phenylephrine ($40\,\mu g\,kg^{-1}$) (■); nicergoline ($400\,\mu g\,kg^{-1}$) (○); phenylephrine ($40\,\mu g\,kg^{-1}$) + nicergoline ($400\,\mu g\,kg^{-1}$) (□). ***$P<0.001$; **$P<0.01$ in respect to corresponding control value (Wilcoxon test).

Effects of propranolol, yohimbine and noradrenaline administered alone or in association

As shown in Table 2, blockade of all β-adrenoceptors with Prop ($2400\,\mu g\,kg^{-1}$), decreased both the amplitude and the duration of uterine contractions,

Table 2 Effect of propranolol (Prop), yohimbine (Yoh), phenylephrine (PE) and noradrenaline (NA) on amplitude and duration of uterine contractions in the pro-oestrous rat

Group of rats	*Agents used and dose* ($\mu g\,kg^{-1}$)	*No of rats* (*n*)	*Amplitude of contractions* (%) *Range*	*Mean ± s.e.*	*P**	*Duration of contractions* (s) *Range*	*Mean ± s.e.*	*P**
1	C: Saline	10	73–128	100 ± 5.3	—	34–70	50 ± 5.0	—
	Prop 800	10	78–126	102 ± 3.8	NS	31–68	46 ± 3.8	<0.05
	Prop 1200	9	70–122	93 ± 6.5	NS	30–60	47 ± 4.0	<0.05
	Prop 2400	9	51–93	72 ± 5.4	<0.001	31–63	46 ± 4.0	<0.05
2	C: Saline	10	79–118	100 ± 3.6	—	35–59	44 ± 2.4	—
	Yoh 1000	9	39–81	†68 ± 4.6	<0.005	29–64	43 ± 3.4	NS
3	C: Saline	9	77–136	100 ± 4.9	—	30–62	45 ± 3.8	—
	Prop 2400	9	50–127	76 ± 7.2	<0.005	28–59	40 ± 4.5	<0.05
	Yoh 1000	8	63–149	†116 ± 7.4	NS	25–60	39 ± 3.6	<0.025
	PE100	8	117–154	145 ± 3.6	<0.001	29–57	39 ± 2.9	<0.025
4	C: Saline	7	65–137	100 ± 7.9	—	37–62	49 ± 4.4	—
	NA 600	7	37–102	††67 ± 11.6	<0.001	26–77	54 ± 9.9	NS
5	C: Saline	8	70–139	100 ± 6.9	—	48–81	67 ± 2.8	—
	Prop 800	7	76–137	104 ± 3.3	NS	44–114	64 ± 3.9	NS
	NA 600	7	84–132	††101 ± 2.6	NS	70–202	112 ± 4.2	<0.005

C = control; NS = non-significant. Animals involved in the same group after saline were administered successively the drug(s) listed at intervals of 30 min. *Values were obtained using Wilcoxon non-parametric statistics. Significantly different, †$P<0.001$; Student's t test; ††$P<0.05$; Student's t test.

whereas blockade of α_2-adrenoceptors, with Yoh, had an inhibitory effect on the myometrium in terms of amplitude (see group 2), but did not affect duration.

Following the Prop-induced uterine relaxation, blockade of the α_2-adrenoceptors by Yoh not only brought back uterine contractility to its initial level (100%) but caused a 16% increase of its contractile force (i.e. 100 ± 0.9 vs 116 ± 7.4; group 3). A single injection of PE 100 $\mu g\,kg^{-1}$ after blockade of the β_1 and β_2 and α_2-adrenoceptors provoked a 30% increase of the amplitude (group 3).

Infusion of NA alone induced a 33% reduction in the force of contractions (group 4) with an elevation of the baseline level.

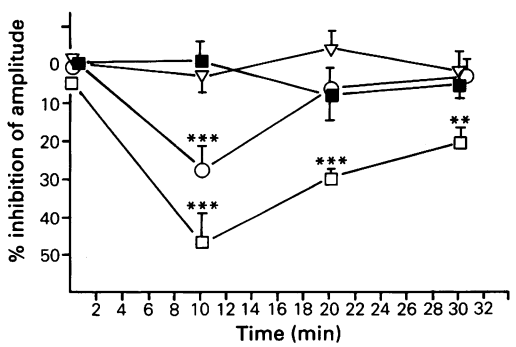

Figure 2 Inhibition (%) of amplitude of spontaneous uterine contraction in response to drug treatment in the pro-oestrous rat; each point represents the mean of 7 values; vertical lines show s.e.mean. Control (▽); phenylephrine (40 $\mu g\,kg^{-1}$) (■); phentolamine (1000 $\mu g\,kg^{-1}$) (○); phenylephrine (40 $\mu g\,kg^{-1}$) + phentolamine (1000 $\mu g\,kg^{-1}$) (□). ***$P<0.001$ in respect to corresponding control value (Wilcoxon test).

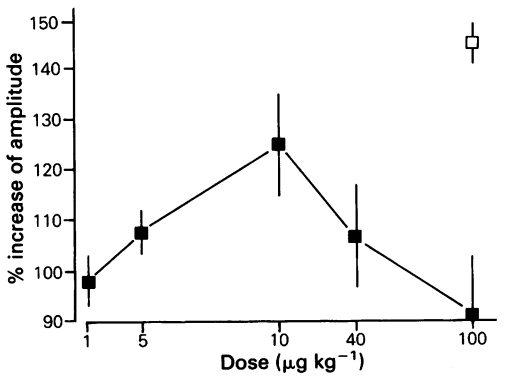

Figure 3 Concentration-effect curve for the % increase of amplitude of uterine contractions induced by phenylephrine. Phenylephrine (■); phenylephrine (100 $\mu g\,kg^{-1}$) + propranolol (2400 $\mu g\,kg^{-1}$) + yohimbine (1000 $\mu g\,kg^{-1}$) (□). Each point is the mean of observations from 4–8 animals and for phenylephrine + propranolol + yohimbine (see Table 2; group 3.); the vertical lines show s.e.mean.

Blockade of the β-adrenoceptors by Prop followed by stimulation of both the α-and β-adrenoceptors by NA modified the myometrial response to NA. In fact a single injection of Prop (800 $\mu g\,kg^{-1}$) abolished the decrease of amplitude normally induced by NA and it also increased the duration of contractions (see group 5).

Discussion

Phenylephrine, a relatively selective agonist of α_1-adrenoceptors (Langer & Shepperson, 1982; Johansson, 1984) was found to enhance myometrial contractile activity in the pro-oestrous rat. It is well established that stimulation of the α_1-postjunctional adrenoceptors produces myometrial contraction through elevation of cytosolic calcium (Ca^{2+}) (Fain, 1984). The excitatory PE-produced effect, observed in the present study was so marked that tetanic contractions were developed in some animals even at the lowest concentration of PE used. The uterine contracture increased with increase in dose, resulting in elevation of the baseline, diminution of amplitude and increase in duration of uterine contraction. Similarly, Hawk & Conley (1985) reported a PE-induced elevation of the baseline in sheep uterine muscle.

The inhibitory effect of the potent α_1-adrenoceptor antagonist nicergoline, (Huchet *et al.*, 1981) on the amplitude of myometrial contraction in the PE-primed rat was more pronounced than that observed without prior exposure of the uterus to the α-receptor stimulant (see Figure 1 and Table 1). The excitatory effect of PE on the myometrium and the subsequent relaxation induced by NI further support the involvement of α_1-adrenoceptors in the mechanism of uterine contraction (Ishikawa & Fuchs, 1978; Exton, 1981). However, NI did not totally overcome the PE-elicited uterine contracture since tetanic contraction not only persisted but was even slightly strengthened, indicating that an α_1-adrenoceptor mediating effect on the contracture should be ruled out.

Similarly, phentolamine, a well known competitive α_1 and α_2-adrenoceptor antagonist (Langer *et al.*, 1985), greatly relaxed the PE pretreated myometrium. We suggest that the reason for this is that when α_2-adrenoceptors are blocked by Phent, they are ineffective in stopping NA release; thus NA can freely flow into the synaptic cleft and consequently stimulate the β_2- postjunctional adrenoceptors, which are known to be myorelaxant (Starke, 1977; Exton, 1981). Hence, the Phent evoked inhibitory effect could be considered as a β_2-mediated relaxation. The fact that uterine mechanical activity in the PE-primed rats returned to control level at the end of Phent treatment (see Figure 2, 20–30 min) seems to reveal a transitory blocking effect of Phent on the α_1-postjunctional adrenoceptors.

Doxey *et al.* (1977) suggested that prejunctional and postjunctional α-adrenoceptors differ in their sensitivity to α-adrenoceptor antagonists and reported that Phent was shown to be more potent in blocking pre- than postjunctional α-receptors. Because Phent, in contrast to NI, abolished the PE-generated tetanic contractions, it is tempting to think of a possible involvement of α_2-postsynaptic excitatory adrenoceptors in this contraction. In fact, both subtypes α_1 and α_2- can be present postjunctionally on vascular smooth muscle (Docherty & McGrath, 1980; Kobinger & Pichler, 1980) and both may induce contraction (Exton, 1985). To our knowledge, as yet there have been no studies demonstrating the existence of α_2-postjunctional adrenoceptors in the uterus. However, according to the model for regulation of uterine contractility by catecholamines proposed by Fain (1984), α_2-postjunctional adrenoceptors mediate contraction by lowering of cyclic AMP. If Fain's model were proved true, then Phent would on one hand prevent the cyclic AMP lowering via the α_2-adrenoceptors and on the other hand Phent would not allow Ca^{2+} movements in the cell through its action on the α_1-adrenoceptors. In this way one could explain both, the Phent-induced abolition of uterine contracture (α_2-action) and its inhibitory effect on the amplitude of uterine contractions (α_1-action). Moreover, other mechanisms could be involved in the induction of uterine contracture by PE. Quaas & Zahradnik (1985), working on human myometrium, demonstrated that α-adrenoceptor stimulation increases the production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_2, both of which are uterotonic substances shown to be synthesized and released by the rat uterus (Chaud *et al.*, 1986). In addition, the last authors reported that Phent inhibits the synthesis of PGE_2 by the rat uterus, an effect that could explain the abolition by Phent of uterine contracture observed in this study.

In order to reinforce the results reported here relative to α_1 adrenoceptor action on the uterine muscle, the β-adrenoceptors were blocked by Prop, while the α_2-adrenoceptors were blocked by Yoh, (see Table 2). Prop exerted an inhibitory action on the uterine muscle only when it was administered at the highest concentration used.

The diminution of the amplitude of uterine contractions following the administration of Yoh could be explained by its antagonist effect on the α_2-adrenoceptors (Doxey *et al.*, 1977) which would lead to an increase of endogenous NA. In addition, however, it has been reported by Lambert, *et al.* (1978) that Yoh antagonizes the contractile action of 5-hydroxytryptamine (5-HT) in the rat fundal strip. Nevertheless, since to our knowledge contraction of uterine muscle by endogenously released 5-HT has not yet been demonstrated, in the present experiments the elevation of uterine activity observed in rats pretreated with

Prop and Yoh, may be best explained by the excitatory effect of the endogenously released NA upon α_1-postjunctional receptors (Kalsner & Quillan, 1984; Langer *et al.*, 1977; 1985). This assumption is strengthened by our observation of further augmentation of amplitude of uterine contraction, subsequent to a single PE injection. It is also of interest to note the absence of PE-produced tetanic contractions after prior blockade of both the β- and the α_2-adrenoceptors (Table 2; group 3). In contrast, stimulation of α-excitatory adrenoceptors by exogenous NA combined with administration of Prop brought about tetanic contractions comparable to those induced by PE (Table 2, group 5) alone. These findings reinforce our preceding suggestion concerning the implication of possible α_2-postjunctional adrenoceptors in the contracture phenomenon.

In conclusion, the findings of the present investigation provide good evidence for the involvement of α-adrenoceptors in the control of uterine contractility in the pro-oestrous rat.

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