Evidence for a noradrenergic transmission in the control of parturition in the rat

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Summary. 6-Hydroxydopamine, when injected at 14:00 h on Days 21 and 22 of pregnancy in the rat (2×50 mg/kg), markedly decreased plasma and uterine noradrenaline concentrations (-60% and -82% respectively; $P < 0.001$). As a consequence of this treatment, there was severe disturbance in the distribution pattern of parturitions: 61% of rats had suppressed parturition and 31% of rats displayed a lengthened or interrupted labour. A bolus dose of prazosin (3 mg/kg) administered at 12:00 h on Day 22 completely blocked the normal process of parturition throughout the next 6 h, a result which is compatible with the half-life of the drug (2.9 ± 0.8 h). Administration of phentolamine (3 mg/kg) at term induced a significant decrease of uterine activity (frequency $\times$ duration of bursts of spike potentials) as revealed by electromyographic recordings *in vivo*. These results suggest that noradrenaline released from sympathetic nerve terminals interacts with α -adrenoceptors located post-synaptically to improve the overall excitability of the myometrium at the onset of labour.

Introduction

Before delivery, the electrical activity of the rat myometrium, measured *in vitro* (Bengtsson, Chow & Marshall, 1984) or *in vivo* (Legrand & Maltier, 1981a), is greatly enhanced. This change is necessary for normal parturition, because if it does not occur delivery is abnormal or delayed (Anderson, Kawarabayashi & Marshall, 1981; Legrand & Maltier, 1981a).

In vitro, it has been widely reported that catecholamines modify the electrical and mechanical responses of smooth muscle from pregnant rat uteri (Abdel-Aziz & Bakry, 1973; Kawarabayashi & Osa, 1976; Osa & Watanabe, 1978; Chow & Marshall, 1981). One objective of the present study was to determine whether the noradrenergic transmission via action on post-synaptic α -adrenoceptors of the myometrium is a physiological regulatory mechanism of parturition in the rat.

In the uterus of the late pregnant rat, noradrenaline is the major catecholamine (Arkinstall & Jones, 1985) and 80% originates from the sympathetic nerves that innervate smooth muscle cells (J. P. Maltier & C. Legrand, unpublished results). Although the uterine concentration of noradrenaline is reduced in the last third of pregnancy in the rat, a result which is in agreement with previous reports on uteri of pregnant rabbits, guinea-pigs and women (Thorbert, 1979; Thorbert, Alm, Björklund, Owman & Sjöberg, 1979; Arkinstall & Jones, 1985), adequate methods for analysis of the turn-over rate of the neurotransmitter indicate that it is greatly enhanced just before delivery (J. P. Maltier & C. Legrand, unpublished results). This observation is a reliable index of neuronal activity in the rat uterus at term. On the basis of such a consideration, we suspect that noradrenergic transmission is maintained in the late pregnant rat myometrium despite severe reduction in tissue levels of noradrenaline. Maltier, Legrand & Corazza (1984) have postulated that an excitatory effect of noradrenaline, mediated via the myometrial α_1 -adrenoceptors, is probably implicated in uterine contractility of parturient rats because a significant increase ($+65\%$) of the α_1 -receptor concentration is observed at parturition.

The present experiments were designed to determine the effects of 6-hydroxydopamine, phentolamine or prazosin treatment on parturition in rats to investigate the role of uterine noradrenergic transmission. The neurotoxin 6-hydroxydopamine has been shown to produce a long-lasting depletion of noradrenaline from various peripheral organs and a functional failure of transmission at sympathetic nerve ends (Malmfors & Sachs, 1968; Thoenen & Tranzer, 1968; Jonsson & Sachs, 1970; De Champlain & Nadeau, 1971). Phentolamine is a selective antagonist of α -adrenoceptors (Ruffolo, 1984) and prazosin is a powerful post-synaptic α -adrenergic blocking agent (Cambridge, Davey & Massingham, 1977; Doxley, Smith & Walker, 1977; Cavero & Roach, 1980; Ruffolo, 1984).

Materials and Methods

Animals

Female Sprague–Dawley rats weighing between 250 and 300 g were used. They were housed in a room controlled for light (10 h light and 14 h darkness with the lights on from 08:00 to 18:00 h) and temperature (22°C) and had free access to food and water. The females were caged with males overnight and successful mating was determined by the presence of spermatozoa in the vaginal smear (Day 1 of pregnancy).

Treatments

Group 1. At 14:00 h on Days 21 and 22 of pregnancy 85 animals were injected intraperitoneally with 6-hydroxydopamine (6-OHDA) hydrobromide (Sigma, St Louis, MO, U.S.A.), 5 mg/100 g body weight, dissolved in 0.9% (w/v) NaCl solution containing 10 mg ascorbic acid/ml (Group 1A). Sixty-two of these treated rats were used to control the effect of 6-OHDA on the process of delivery. The other rats were killed by cervical dislocation at 16:00 h on Day 22 of pregnancy for catecholamine assays.

A control group (1B) of 42 animals received vehicle only: 20 females were used to control the effect of treatment on delivery and the others were killed at 16:00 h on Day 22 for catecholamine assays.

Group 2. At 12:00 h on Day 22 of pregnancy, 20 females were injected subcutaneously with a single bolus dose of 1 mg prazosin-HCl (Pfizer, Belgium) dissolved in a 0.05 M-Tris-HCl, 0.01 M-MgCl₂ buffer with 2.5% ethanol (Group 2A).

A control group of 20 females received vehicle only (Group 2B). All the rats were allowed to litter.

Group 3. Eighty-five pregnant rats were left untreated and were distributed as follows: 22 females were killed for catecholamine assays at 10:00 h on Day 22 and at 16:00 h on Day 22 of pregnancy. The remaining rats were allowed to litter.

Group 4. Electromyographic activity was recorded by means of bipolar electrodes inserted into the myometrium, at the ovarian and cervical ends of each uterine horn, on Day 19 of pregnancy. The electrodes were constructed from isolated stainless wires (nickel–chrome blending 80/20) with a cross-section of 80 μ m. The distal tips of the wires were bared for a distance of 1 mm and inserted, 3–5 mm apart, between the antimesometrial and mesometrial poles of the uterus. The electrodes were exteriorized via an incision over the head. Signals were amplified using an ink-writer polygraph (E.C.E.M.) with a time constant of 0.1 sec.

Recordings were started on Day 21 of pregnancy. The overall operative procedure had no deleterious effect upon pregnancy and all the rats littered normally between 12:00 h on Day 22 and 12:00 h on Day 23 which is the normal range for parturitions in our breeding colony. During all

recording sessions, animals were allowed to move freely in their cage and received water and food *ad libitum*. Three types of experimental animals were used: 9 females were left untreated after surgical procedures to detect normal activity of the myometrium; 4 rats were injected intraperitoneally at the time of vaginal bleeding with a bolus dose of 1 mg phentolamine (2-([*N*-(*m*-hydroxyphenyl)-*p*-toluidino]-methyl)-2-imidazoline methane sulphonate; Ciba-Geigy, Basle, Switzerland) dissolved in 1 ml 0.9% (w/v) NaCl; and 4 rats were treated with 1 ml saline and served as controls for the phentolamine-injected animals.

All females allowed to litter normally (Groups 1A, 1B, 2A, 2B and 3) were autopsied after 12:00 h on Day 23 to determine whether parturitions were complete or partial.

Assay methods for noradrenaline

Peripheral blood was collected into heparinized flasks and centrifuged at 5000 *g* for 5 min at 0–4°C. Then, plasma was mixed (v/v) with ice-cold 0.6 N-perchloric acid. After mixing, the acidified plasma was centrifuged at 4°C for 5 min at 27000 *g* and the supernatant fraction was taken for noradrenaline assay. Immediately after blood collection, uteri were isolated, defatted, weighed and homogenized in 10 volumes (w/v) ice-cold 0.3 M-perchloric acid with 0.1% ascorbic acid with an Ultra-Turrax homogenizer. The homogenate was centrifuged at 4°C for 5 min at 27000 *g*. The supernatants were frozen and stored in liquid nitrogen before noradrenaline assay.

Plasma and uterine noradrenaline were assayed by the radioenzymic procedure of Da Prada & Zürcher (1976). Noradrenaline was assayed in duplicate using 100 µl plasma or uterine supernatants. The noradrenaline was converted to its O-methylated labelled derivative (normetanephrine) by catechol-O-methyl transferase (COMT) in the presence of tritiated-*S*-adenosyl methionine (Radiochemical Centre, Amersham, U.K.; sp. act. 73 Ci/mmol). COMT was purified from rat liver by the method of Axelrod & Tomchick (1958). The normetanephrine was then extracted and isolated by thin-layer chromatography. The tritiated normetanephrine was scraped off, converted to vanillin by periodate cleavage and thereafter extracted into toluene. The radioactivity was measured by liquid scintillation counting in an Inter technique spectrometer (Inter technique SL 3000). Assay sensitivity was 4 pg/ml for plasma or uterine supernatant. Interassay coefficient of variation was 5% and intra-assay variation was 8%.

Statistical analysis

Results are expressed as mean values $\pm$ s.e.m. Statistical significance was determined by using Student's *t* test with paired comparisons when appropriate or χ^2 analysis (Snedecor & Cochran, 1957).

Results

Noradrenaline concentrations in plasma and uterine tissues in 6-OHDA-treated rats

By 2 h after the second injection of 6-OHDA (16:00 h on Day 22) plasma and uterine noradrenaline concentrations were greatly depleted (Fig. 1). Plasma noradrenaline was 8.2 ± 1.0 pg/ml compared with 22.2 ± 2.1 pg/ml in control rats ($P < 0.001$). Uterine noradrenaline was 1.3 ± 0.4 ng/g compared with 7.4 ± 1.4 ng/g in controls (reduction of 82%, $P < 0.001$).

Delivery patterns in normal and treated rats

Untreated rats. The events of labour were recorded by continuous observation. The delivery of the first young was considered as the onset of parturition. The duration of parturition was estimated as the time from the delivery of the first to the last young of a litter.

Fig. 1. Noradrenaline concentrations in plasma (a) and uterine tissues (b) in control rats killed at 10:00 h on Day 22 (open column) or at 16:00 h on Day 22 (stippled column) and in 6-OHDA-treated rats killed at 16:00 h on Day 22 (dark column). Each value represents the mean $\pm$ s.e.m. for the number of animals indicated. ★ significantly different from previous stage of pregnancy $P < 0.01$ (t test).

In our breeding colony normal pregnant rats gave birth between 12:00 h on Day 22 and 12:00 h on Day 23. Under our lighting schedule most of the parturitions were spread over a short period, with 75% occurring between 12:00 h and 19:00 h on Day 22 (Fig. 2).

Duration of delivery was 94 ± 10 min in the group of untreated rats (Group 3). When duration of parturition exceeded 2 h delivery was considered abnormal.

6-OHDA-treated rats. Immediately after the first injection of 6-OHDA, the rats showed transient signs of sympathomimetic stimulation (e.g. hair erection) which was much less pronounced after the second dose.

The distribution of parturitions in 6-OHDA-treated rats (Group 1A) is presented in Fig. 3. In this treatment group the percentages of delivering rats were greatly modified in comparison with

Fig. 2. Time of parturitions in normal pregnant rats (Group 3) exposed to a lighting schedule of 10 h light, 14 h darkness.

Fig. 3. Percentages of delivering rats (a) and cumulated percentages of parturitions (b) between 12:00 h on Day 22 and 12:00 h on Day 23 of pregnancy in 6-OHDA-treated rats (Group 1A, dark column: abnormal parturitions; open column: normal parturitions) and vehicle-injected rats (Group 1B, stippled column). ☆ significantly different from Group 1B value $P < 0.05$ (χ^2 analysis).

Fig. 4. Cumulated percentages of parturitions in rats injected with prazosin (Group 2A, dark column) or vehicle (Group 2B, stippled column) and in normal pregnant rats (Group 3, hatched column). ☆ significantly different from Group 2B value, $P < 0.05$; ☆ significantly different from Group 3 value, $P < 0.01$ (χ^2 analyses).

Fig. 5. Electromyographic recording of uterine activity in a conscious unrestrained rat (Group 4). Upper tracing: ovarian end of the uterus. Lower tracing: cervical end of the uterus. (a) 30 h before birth; (b) 2–15 min before birth (vaginal bleeding).

control rats injected with vehicle only (Group 1B). In 6-OHDA-treated rats, only 8% of deliveries were completely normal; 61% of the rats had suppressed delivery and 31% of animals displayed lengthened (10%) or interrupted (21%) labour.

Prazosin-treated rats. After a bolus dose of prazosin, none of the treated rats had normal parturition between 14:00 h on Day 22 and 18:00 h on Day 22, whereas 30% of control rats injected with vehicle alone displayed normal parturition between 14:00 h and 18:00 h on Day 22 (test χ^2 : $P < 0.01$; Fig. 4). Later there was no difference between the two groups of rats. Moreover, vehicle injected at 12:00 h on Day 22 significantly reduced the frequency of deliveries when compared with normal untreated rats.

In-vivo recording of electromyographic activity (EMG)

EMG activity was estimated as the average duration of electrical events per hour. A typical pattern of electrical activity recorded at Days 21 and 22 of pregnancy is shown in Fig. 5. Short bursts of spike potentials occurred irregularly and there was no precise relationship between the activity recorded at each end of the uterus. At parturition, electrical bursts were more synchronized and their duration, frequency and amplitude were increased (Fig. 5).

As illustrated in Fig. 6, three major phases could be distinguished in the changes of uterine activity that occurred during the last 36 h before delivery. Up to 16 h before birth the activity remained fairly stable. Then, the activity increased progressively during the next 10 h. During the last 6 h of pregnancy there was a sharp increase of activity which culminated when the first young was expelled. A similar evolution of electrical activity was seen at the cervical and ovarian ends of uterine horns (Table 1). The amplitude of the spike potentials was increased progressively in the last 10 h before birth, with a marked increase at the cervical end of the uterus (Table 1).

Fig. 6. Electrical activity (frequency $\times$ duration of the bursts of spike potentials) at the cervical extremity of the uterus in normal untreated rats (solid line) during the last 36 h of pregnancy, and after injection of phentolamine (broken line) or vehicle (stippled line). The arrow indicates the time of injection of phentolamine or vehicle. Values are mean $\pm$ s.e.m. $\star$ significantly different from untreated or vehicle-injected rats, $P < 0.05$ (t test).

Table 1. Electromyographic characteristics of uterine activity in the late pregnant rat *in vivo*

Hours before birth	Ovarian end of the uterus		Cervical end of the uterus	
	Frequency $\times$ duration of the bursts of spike potentials (min/h)	Amplitude of spike potentials (μ V)	Frequency $\times$ duration of the bursts of spike potentials (min/h)	Amplitude of spike potentials (μ V)
36–30	5.2 $\pm$ 0.3	133 $\pm$ 5	4.2 $\pm$ 0.3	102 $\pm$ 16
30–25	4.4 $\pm$ 0.3	111 $\pm$ 4	3.8 $\pm$ 0.4	130 $\pm$ 11
25–20	4.7 $\pm$ 0.3	109 $\pm$ 8	2.8 $\pm$ 0.4	148 $\pm$ 12
20–15	5.0 $\pm$ 0.2	121 $\pm$ 10	3.1 $\pm$ 0.6	129 $\pm$ 11
15–10	6.8 $\pm$ 0.4	140 $\pm$ 6	5.8 $\pm$ 0.8	115 $\pm$ 28
10–6	9.2 $\pm$ 0.9*	141 $\pm$ 15	7.3 $\pm$ 1.1	152 $\pm$ 10
6–1	21.2 $\pm$ 2.6*	145 $\pm$ 5	18.2 $\pm$ 2.3*	183 $\pm$ 17
Vaginal bleeding	34.8 $\pm$ 5.4*	—	32.5 $\pm$ 3.2*	—
Birth	35.2 $\pm$ 4.5	233 $\pm$ 44	30.5 $\pm$ 4.1	275 $\pm$ 30*

Values are mean $\pm$ s.e.m. for 9 rats.

*Significantly different from previous stage of pregnancy $P < 0.05$ (t test).

Injections (s.c.) of 1 mg phentolamine at the time of vaginal bleeding produced in the next 30 min a significant inhibition of the duration of the uterine activity ($P < 0.001$) which was not observed after vehicle administration (Fig. 6). The amplitude of the spike potentials measured at the cervical end of the uterus was unaffected by the drug administration: it remained at $249 \pm 23 \mu\text{V}$ 10 min after treatment and was successively 241 ± 79 , 268 ± 76 , 234 ± 50 and $234 \pm 68 \mu\text{V}$ in the next 20, 40, 50 and 60 min.

Discussion

The results presented in this paper disclose a rapid and drastic reduction of endogenous noradrenaline concentrations in both plasma and uterus produced by 6-OHDA (respectively -60% and -82%). This treatment ($2 \times 50 \text{ mg/kg}$, 24-h interval) was chosen to obtain a consistent long-lasting disappearance of endogenous noradrenaline (Thoenen & Tranzer, 1968). The noradrenaline depletion caused by 6-OHDA could be due to a selective destruction of the noradrenergic nerve terminals (Tranzer & Thoenen, 1967; Malmfors & Sachs, 1968). According to Jonsson & Sachs (1970) 6-OHDA may act as a 'false neurotransmitter' which displaces noradrenaline from its binding sites (Thoenen & Tranzer, 1968). Whatever the precise mechanism of action of 6-OHDA, the drug produces an effective sympathectomy. This result is in agreement with previous data of Thorbert, Alm, Owman, Rosengren & Sjöberg (1978) on the cyclic guinea-pig uterus. The very marked disturbance in the distribution of the moment of parturition that we found could be considered a consequence of the treatment: only 8% of rats had completely normal delivery, 61% of the remaining rats had entirely suppressed parturitions, the other rats presenting partial or lengthened deliveries. Our results with adrenoceptor blocking agents (prazosin or phentolamine) provide indirect evidence that the normal process of delivery is probably related to the subsequent interaction of the noradrenaline with α -excitatory adrenoceptor sites in the myometrium. The characteristics of α -adrenoceptors present on the cell surface of preparturient rat myometrium have been reported by Maltier *et al.* (1984). The numbers of myometrial α -adrenoceptors, which mediate uterine contractions, are increased in the last 6 h of pregnancy (Maltier *et al.*, 1984), a time when the activity of the uterus (EMG recordings *in vivo*) appears greatly enhanced. Prazosin, a powerful α_1 -adrenoceptor antagonist (Ruffolo, 1984), selectively blocks post-junctional excitatory α_1 -adrenoceptors, without acting upon the pre-junctional α_2 -adrenoceptors which regulate the noradrenaline release via a negative feed-back mechanism (Cambridge *et al.*, 1977; Caverio & Roach, 1980; Kobinger, 1984). In our experimental conditions, a bolus dose of prazosin postponed delivery during the 6 h after its administration but not later: between 12:00 h and 18:00 h on Day 22 none of the prazosin-injected rats delivered, but 62% exhibited normal delivery between 18:00 h on Day 22 and 12:00 h on Day 23. This observation is in good agreement with the half-life of the drug which has been estimated as $2.9 \pm 0.8 \text{ h}$ (Jaillon *et al.*, 1979; Baughman *et al.*, 1980; Timmermans & Van Zwieten, 1984). The vehicle used for prazosin injection also disturbed the normal process of delivery but from 14:00 h until 18:00 h on Day 22 the cumulated percentages of parturitions remains significantly decreased in prazosin-treated rats as compared to vehicle injected rats, thus demonstrating an action of the drug in preventing the normal process of labour. These results suggest that a transient blockade of myometrial α_1 -excitatory adrenoceptors may be responsible for the transient inhibitory action of prazosin on the course of labour. In the next 2 h after injection of vehicle only, suppressed deliveries were associated with a significant reduction in the number of α_1 -adrenoceptors of the myometrium (-60% , $P < 0.01$; C. Legrand, J. P. Maltier & M. J. Bosc, unpublished results). Later, in this treatment group, the number of α_1 -adrenoceptors is gradually increased (unpublished results) and at the same time deliveries are starting off. Thus, in agreement with the previous work of Bosc & Nicolle (1979), the injection of vehicle applied just before the onset of labour is a stress which delayed the time of birth of the first young. The effect of the stress induced by vehicle-injection can be attributed to the

changes of catecholamine levels (Legrand & Maltier, 1981b) and/or to the decrease of myometrial α_1 -adrenoceptors density, both factors regulating uterine activity. The hypothesis concerning the involvement of a noradrenergic transmission in the control of myometrial function at term was investigated by in-vivo recordings of myometrial activity in rats injected with phentolamine. Phentolamine, a non-selective $\alpha_1 + \alpha_2$ -adrenoceptors antagonist, interferes with the release of endogenous noradrenaline via a presynaptic (α_2) mechanism but antagonizes the postsynaptic α_1 -adrenoceptor mediated responses of the myometrium. As could be expected from earlier observations of Rüsse & Marshall (1970), phentolamine administered in preparturient rats produced marked EMG activity (culminating in vaginal bleeding) and a marked but transient fall in electrical activity.

Such an inhibition of spontaneous activity of the uterus after phentolamine has been reported for the rhesus monkey (Harbert & Spisso, 1981). In these conditions it is possible that the sudden increase in EMG activity of the uterus 4–6 h before the expulsion of the first young may be elicited by α -stimulatory noradrenergic transmission which then could intensify the uterine sensitivity to oxytocin (Rüsse & Marshall, 1970) and elicit strong uterine contraction (Bengtsson *et al.*, 1984). This concept supports the finding of Fuchs & Poblete (1970) that prolonged administration of oxytocin in the late pregnant rat could not induce labour earlier than 4–6 h before the expected term. We suppose that this noradrenergic potentiation may be due to the effects of the neurotransmitter in prolonging the plateau potential in oestrogen-dominated myometrial cells (Kawarabayashi & Osa, 1976; Osa & Watanabe, 1978) of the preparturient rat.

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