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PLASMA OXYTOCIN AND OXYTOCIN NEURONE ACTIVITY DURING DELIVERY IN RABBITS

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SUMMARY

1. The extracellular electrical activity of magnocellular neurones was recorded from unanaesthetized, unrestrained rabbits in birth and the post partum suckling period. The activity of oxytocin neurones was differentiated from that of vasopressin cells on the basis of their stereotyped activity in suckling.

2. Oxytocin neurones showed five to fourteen discrete bursts of accelerated discharge in parturition. Each burst lasted 2–22 s and represented a 3–100-fold increase in the rate of firing, compared with pre-partum values, and was followed 10–34 s later by delivery. After parturition, the spontaneous activity of these neurones returned to pre-partum rates of firing.

3. Vasopressin neurones did not show any bursts of discharge in delivery. There was a significant fall in the discharge frequency compared with pre-partum levels ($P < 0.05$: Student's t test) and a significant ($P < 0.01$) lengthening of the modal interspike interval.

4. Serial blood samples were obtained during parturition in ten rabbits. Simultaneous recordings of magnocellular neurones activity and plasma oxytocin measurements were made in four of these experiments. Plasma oxytocin profiles were related to the observed events of parturition.

5. Frequent blood samples (0·2–0·3 ml every 10–15 s) were taken throughout delivery and plasma oxytocin measured by sensitive radioimmunoassay in unextracted plasma (lower limit sensitivity of assay 5 pg ml^{-1}).

6. Before birth, plasma oxytocin was 53 ± 12 pg ml^{-1} (mean $\pm$S.E. of mean) and rose to 2846 ± 326 pg ml^{-1} within 40–120 s of the onset of the expulsive phase of delivery. Peak concentrations of oxytocin were coincident with delivery of the first or second fetus.

7. No sign of pulsatile release of oxytocin was demonstrated in the profiles but significantly ($P < 0.001$) greater variance in oxytocin titres was found during birth compared with pre-partum values which is suggestive of pulsatile release. There was a straight line relationship between peak oxytocin concentrations in the plasma and the speed of delivery, implying that oxytocin facilitates as well as maintains labour in the rabbit.

INTRODUCTION

There is still debate about the importance of oxytocin in the initiation and maintenance of labour (Fuchs, 1983). In particular, evidence concerning the electrical activity of oxytocin neurones in birth is contradictory. Boer & Nolten (1978), working in the anaesthetized rat, reported that birth was accompanied by a slight, but statistically significant, rise in the firing rate of the magnocellular neurones, whereas Summerlee (1981), recording from unanaesthetized rats, claimed that the oxytocin neurones discharged with high-frequency bursts in delivery. Each burst of discharge was related either to forceful abdominal straining or expulsion of a fetus or placental material. However, there is no direct evidence to show that the reported changes in oxytocin neurone activity result in a rise in plasma oxytocin. Therefore, experiments were done to answer two questions: (1) is the activity of oxytocin neurones reported in the rat during birth different from the discharge of oxytocin neurones in the rabbit? (2) Is there a definite relationship between changes in the firing pattern of oxytocin neurones and the levels of plasma oxytocin during birth in the rabbit?

METHODS

Experiments were carried out on thirty-six female Californian rabbits which were bred in the department and housed in a free-range run, under natural lighting conditions. Twenty-nine rabbits were implanted with flexible microwire recording electrodes into the paraventricular nucleus of the hypothalamus and a stimulating electrode into the stalk of the neurohypophysis similar to the method described by Paisley & Summerlee (1984). A further four rabbits were implanted with recording electrodes into the lateral hypothalamic area and another three animals with electrodes in the parietal area of the cerebral cortex for control recordings. Ten of the rabbits implanted with paraventricular recording electrodes were fitted, at a later stage, with an indwelling jugular cannula (Tygon tubing 2 mm o.d., $< 0{\cdot}5$ mm i.d.). They were re-anaesthetized with ketamine (Vetalar, Parke-Davies: $1{\cdot}5$ mg kg^{-1}) and xylazine (Rompun, Bayer: 3 mg kg^{-1}), the jugular cannulated, and the free-end of the cannula run subcutaneously around the neck, to emerge through a small incision between the ears. The rabbits were allowed to recover. Each cannula was flushed twice daily with a sterile solution of heparin (Pularin, Duncan, Flockart & Co. Ltd.: 5000 u. ml^{-1}) and the free-end sealed with a sterilized stainless-steel pin. During an experiment an additional length of tubing was attached to the cannula and this tube suspended above the animal's cage to allow her freedom of movement. Dead space within the tube and cannula was $< 0{\cdot}2$ ml.

Neuronal activity in birth

The rabbits were time mated, brought into the laboratory, and caged individually 5 days before the expected day of parturition (Lincoln, 1971). Electrical activity was tested on each electrode and two electrodes chosen as suitable for differential recordings during birth. Single-unit activity was judged by criteria similar to those used by Burns & Webb (1976). Neuronal activity was recorded on an FM channel of a tape recorder (Racal Store 7D) for subsequent analysis. Control records, 5–10 min duration, were made intermittently throughout the first three days in the laboratory for comparison with activity during and after birth. The rabbits were watched continuously for the last 48 h before the expected time of parturition and 5 min samples of record taken every half-hour during this period.

The expulsive phase of birth was usually, but not always, preceded by a particular pattern of behaviour with periods of intense nest building, fur pulling and panting, followed by one or two abdominal straining movements. Neuronal activity was monitored continuously during the expulsive phase of birth and continued after parturition until suckling in the post partum period was completed (usually within 20 min of the end of delivery).

Neuronal activity was not analysed at the time of recording. Magnetic tapes were replayed and

a voltage gate set to discriminate individual potentials from background activity. A microprocessor (Apple II) was used to calculate mean frequencies of discharge for the cells and to construct a series of time-interval histograms (de la Mahotiere, Paisley & Summerlee, 1984).

Neuronal activity before, during and after birth and in the subsequent suckling period were compared and related to the observed events of delivery and weight gain of the kittens in nursing. After these experiments, the neurones were tested for evidence of antidromic activation from the neurohypophyseal stalk.

Oxytocin profiles in birth

Blood samples (0·2–0·3 ml) were withdrawn into chilled 1 ml syringes every 10–15 s during the course of labour. Each sample was transferred to a plastic centrifuge tube and stored on ice. After approximately every fifty samples were collected, 10 ml of isotonic saline was infused to restore blood volume. At the end of parturition, usually detected by changes in the behaviour of the doe, sampling was reduced to once every 2–5 min and continued for a maximum of 1 h after delivery. During delivery details of the doe's behaviour, expulsions of kittens and placentae and the timing of blood samples were recorded onto one channel of a tape recorder. Approximately 15 min after samples were taken, they were spun at 2000 ***g*** for 30 min at 4 °C. Plasma from each sample was decanted and stored at −20 °C until assay. Triplicate samples (20–50 μl) of plasma were assayed for oxytocin by radioimmunoassay using the method developed by Robinson (1980). Where single unit activity was present at the time of birth, simultaneous recordings of neuronal activity were taken whilst chronically sampling the blood.

Control experiments on plasma oxytocin

Control experiments were carried out to answer two questions: (1) what were the plasma levels of oxytocin in late pregnancy in the rabbit? (2) Did the sampling regimen used evoke the release of oxytocin? As haemorrhage *per se* releases oxytocin (Fabian, Forsling, Jones & Lee, 1969), it was important to examine whether the protocol adopted in our study caused the release of oxytocin. Blood samples (30–60) were taken from each of three rabbits 4–5 days pre-partum in the same manner as described for delivery. In addition, in two animals, in the middle of this sampling procedure 10 ml of blood were withdrawn rapidly to simulate acute haemorrhage.

Confirmation of the site of the recording electrodes

At the end of the experimental period (10–12 months) the position of the microwire tips that had yielded neuronal activity was confirmed using a Cajal's stain (Summerlee, Paisley & Goodall, 1982).

RESULTS

Extracellular electrical recordings were taken from thirty-five hypothalamic and ten cortical neurones and the pattern of discharge of these cells analysed in relation to the observed events of parturition and reflex milk ejection. Four of the hypothalamic neurones were recorded in birth whilst blood samples were taken for oxytocin assay. In a further six rabbits, blood samples alone were taken during parturition.

Classification of recorded hypothalamic neurones

The hypothalamic neurones were divided into three groups according to their anatomical position and their electrophysiological responses in suckling. Nineteen of the neurones were classed as magnocellular because they were antidromically driven from the neurohypophysis and were later confirmed, by histology, to be in the paraventricular nucleus of the hypothalmus. Three tests, constant latency, frequency following and collision-extinction, were used to validate the antidromic response.

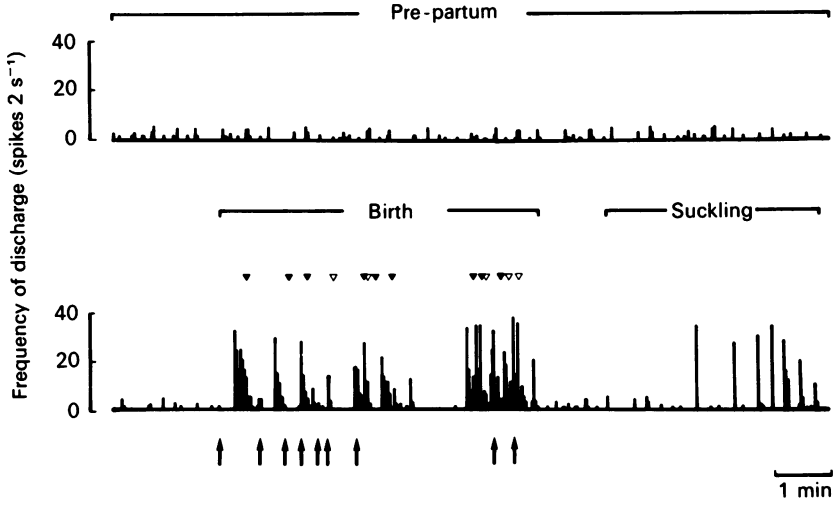

Fig. 1. Analysed data recorded from one antidromically-identified magnocellular neurone during parturition in a conscious rabbit. The histograms are continuous and show the rate of discharge before, during and after parturition. Observed abdominal contractions (↑) and delivery of a fetus (▲) or placenta (△) are superimposed on the histogram. During birth bursts of high-frequency activity lasting 4–16 s were seen, followed 10–18 s later by delivery. In the post partum suckling period seven bursts of accelerated discharge were seen which is typical of the discharge of a rabbit oxytocin neurone during reflex milk ejection.

Each neurone showed a specific latency between the driving stimulus and the antidromic response (mean 15·6 ms: range 8·2–26·4 ms).

The magnocellular neurones were divided into two groups. Group 1 ($n = 8$) showed discrete bursts of high-frequency activity in suckling (Fig. 1), a pattern of discharge typical of putative oxytocinergic neurones during reflex milk-ejection in the rabbit (Summerlee, Paisley, O'Byrne, Robinson & Fletcher, 1985). In contrast, neurones in Group 2 ($n = 11$) showed an over-all decrease in their rate of discharge in suckling and no bursts of activity; they were classed as putative vasopressinergic. The activity of the paraventricular neurones was compared with the discharge of a further sixteen neurones (Group 3) which could not be antidromically activated and were shown later to be in the lateral hypothalmus. A further control group of ten neurones was recorded from the parietal area of the cerebral cortex.

There was a wide range of activity recorded from all the neurones before birth (range 0·01–66 spikes s^{-1}). The rate of discharge and the values of the modal interspike intervals for these cells are given in Table 1. There were statistically significant differences ($P < 0·05$: Mann–Whitney U test) observed between the firing rates and modal interspike intervals for the neurones in Groups 1, 2 and 3.

Activity of magnocellular neurones and birth

The rate and temporal pattern of discharge of all the magnocellular neurones changed in birth. The degree of change for each parameter during and immediately after birth, was expressed as a fraction of the activity of each neurone before birth.

TABLE 1. The temporal pattern of discharge of hypothalamic and cerebral cortical neurones in parturition in conscious rabbits. Records of approximately 7 min, the duration of birth, were used for calculating each entry. The degree of change for each parameter is expressed as a fraction of the value before birth. Note that neurones in Group 1 (putative oxytocinergic cells) showed changes in firing rate and modal interval opposite to those exhibited by Group 2 neurones (putative vasopressinergic cells) and opposite changes for control neurones in lateral hypothalamic area and cerebral cortex. A statistical comparison of these changes is shown in Table 2

	Mean frequencies (spikes s^{-1})			Modal intervals (ms)		
Cell No.	Pre-partum	Birth/ pre-partum	Post partum/ pre-partum	Pre-partum	Birth/ pre-partum	Post partum/ pre-partum
			Magnocellular neurones Group 1			
1a	1·2	3·07	0·72	27·1	0·77	3·86
2a	2·5	3·01	0·98	19·1	0·62	1·00
3a	0·3	9·74	0·99	40·6	0·51	1·00
4a	5·8	2·62	1·05	52·9	0·15	0·84
5a	1·9	4·21	1·00	58·3	0·61	1·00
6a	0·3	8·79	0·48	40·0	0·56	0·62
7a	1·8	1·69	1·00	30·1	0·36	0·98
8a	1·7	4·13	1·71	24·0	0·95	1·17
Mean ±S.D.	1·94±1·74	4·66±2·97	1·00±0·35	36·51±13·95	0·57±0·24	1·31±1·05
			Magnocellular neurones Group 2			
9a	0·23	0·07	0·87	29·0	—	0·87
2b	3·6	0·04	0·62	18·8	2·28	2·68
10a	33·6	0·73	0·99	15·9	1·34	0·99
11a	5·5	0·18	0·38	20·8	2·80	1·75
11b	17·5	0·73	0·89	26·0	1·41	1·01
4b	3·2	0·13	1·72	17·2	3·22	0·75
4c	5·5	0·12	1·79	18·1	2·06	1·17
6b	6·4	0·61	1·17	13·4	1·71	1·33
12a	46·0	0·63	0·81	5·4	1·62	1·07
7b	0·5	0·55	1·23	12·0	1·03	0·99
4d	0·3	0·51	2·69	8·8	0·85	1·00
Mean ±S.D.	11·12±15·22	0·39±0·28	1·11±0·72	16·86±6·96	1·86±0·80	1·24±0·55
			Lateral hypothalamic neurones (n = 16)			
Mean ±S.D.	2·64±2·60	0·32±0·32	1·15±0·35	256·58±313·24	1·78±0·70	1·00±0·24
			Cortical neurones (n = 10)			
Mean ±S.D.	8·88±6·68	1·00±0·18	1·22±0·27	31·84±19·41	2·04±0·87	1·13±0·44

The changes are shown in Table 1 and a summary of the statistical significance of the mean changes in discharge of all the neurones is shown in Table 2.

Superimposed on the spontaneous activity of Group 1 neurones (putative oxytocin cells) were five to fourteen discrete bursts of accelerated discharge during birth (Fig. 1). Each burst lasted 2–22 s and represented a 3–100-fold increase in the rate of firing compared with pre-partum values. The bursts were composed of a series of smaller bursts of higher frequency discharge (Fig. 2) with interspike intervals of < 10 ms, whereas the bursts of activity exhibited by the same neurones during the post partum suckling period were shorter and composed of a single burst of high-frequency discharge (Fig. 2). The consequences of this intermittent activity

TABLE 2. A summary of the significant changes in the temporal pattern of discharge of hypothalamic and cerebral cortical neurones during and immediately after parturition in conscious rabbits

	Mean frequency of discharge		Modal interspike interval	
	Birth/ pre-partum	Post partum/ pre-partum	Birth/ pre-partum	Post partum/ pre-partum
Magnocellular neurones Group 1	$P < 0.01\uparrow$	n.s.	$P < 0.05\downarrow$	n.s.
Magnocellular neurones Group 2	$P < 0.05\downarrow$	n.s.	$P < 0.01\uparrow$	n.s.
Lateral hypothalamic area neurones. Group 3	$P < 0.01\downarrow$	n.s.	$P < 0.01\uparrow$	n.s.
Cerebral cortical neurones	n.s.	$P < 0.02\uparrow$	$P < 0.005\uparrow$	n.s.

Data used to complete this summary are shown in Table 1. Differences between the ratios of firing rate and modal interspike interval from unity were compared using Student's t test. The direction of significant changes is shown by the arrow (n.s. = no significant change seen). Note that magnocellular neurones in Group 1, which showed bursting activity during parturition, showed changes in rate of firing and modal interspike interval opposite to the neurones in Groups 2 and 3.

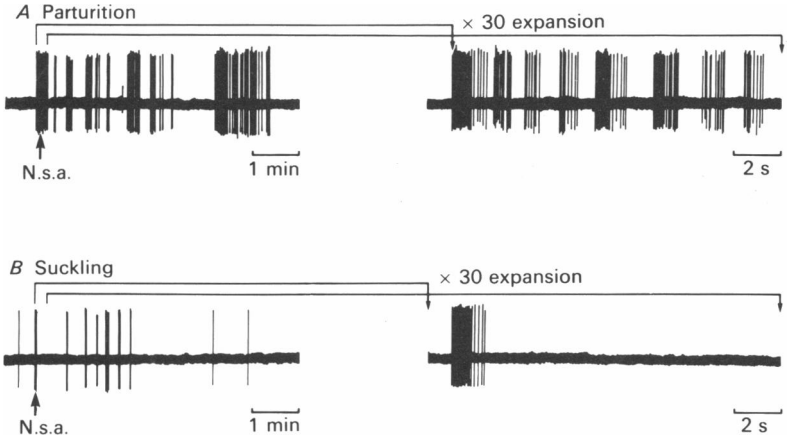

Fig. 2. Two traces of neuronal data recorded from the same magnocellular neurone during birth and suckling in a conscious rabbit. Note the difference between the bursts of neurosecretory activity (N.s.a.) seen in delivery (*A*) and suckling (*B*). The characteristics of these bursts are shown on an expanded time scale on the right. Bursts in parturition were a composite of smaller higher-frequency bursts compared with the single bursts of neurosecretory activity in suckling.

were a significant ($P < 0.01$) increase in the mean firing rate of the oxytocin neurones and a significant ($P < 0.05$) shortening of the modal interspike interval (Tables 1 and 2). The bursts of discharge were temporally related to delivery and were followed 10–34 s later by delivery of a fetus (Figs. 1 and 3). No relationship between forceful abdominal straining and neuronal activity or delivery of placental material was demonstrated.

In contrast, the putative vasopressin (Group 2) neurones did not show any periods

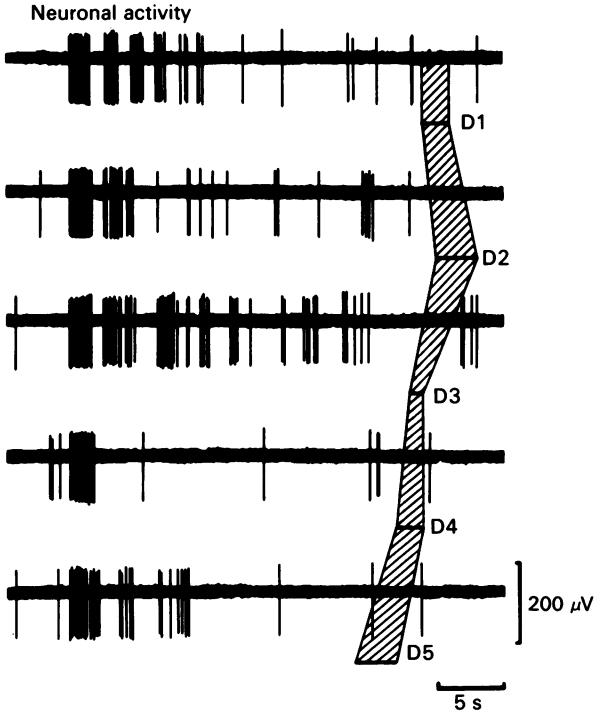

Fig. 3. The activity of one oxytocin neurone, recorded during parturition in a rabbit, to illustrate the temporal relationship between bursts of high-frequency discharge and delivery of young. The traces were aligned at the onset of a burst of activity and delivery (D1–5) is shown by the hatched area. Note that the onset of bursting discharge was fo[illegible] l 22–28 s later by delivery of a kitten.

of accelerated discharge in birth. There was a significant fall in the rate of discharge of these neurones and a significant increase in the average value of the modal interval (Table 2). These changes served to accentuate even further the differences between the physiological responses of the two groups of magnocellular neurones.

Radioimmunoassay technique

Oxytocin measured by radioimmunoassay was found in all samples collected on the day of birth and during parturition. The concentrations ranged from 12 to 3030 pg ml^{-1}, with intra- and interassay co-efficients of variation for mid-range values of 8 and 15 % respectively. The maximum sensitivity of the assay was 5 pg ml^{-1}. Non-specific binding in all assays was found to be low. When high levels of oxytocin were detected, the samples were checked for non-specific interference in the plasma, but in all cases the detected levels of oxytocin were found to be due to oxytocin-like immunoreactivity.

Oxytocin profiles in birth

A significant elevation ($P < 0{\cdot}001$: Student's t test) in mean concentration of plasma oxytocin was seen in all ten rabbits during birth compared with pre-partum

values. Before delivery plasma oxytocin was 53 ± 12 pg ml^{-1} (mean $\pm$S.E.) and rose to 2846 ± 326 pg ml^{-1} within 40–120 s of the onset of the expulsive phase of labour. Peak titres of hormones were coincident with delivery of the first or second fetus. Examples of oxytocin profiles from four rabbits are shown in Fig. 4. The start of the rise in oxytocin levels occurred 35–65 s before delivery of the first fetus. There was

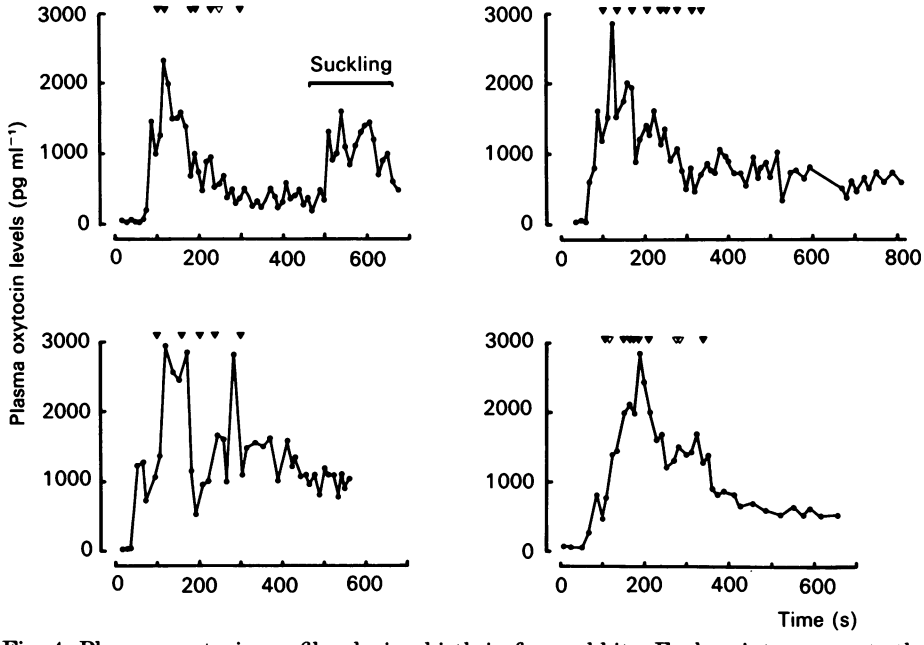

Fig. 4. Plasma oxytocin profiles during birth in four rabbits. Each point represents the average oxytocin concentration in triplicate portions of plasma. The delivery of individual fetuses (▲) and placentae (△) are shown above each profile. Note the overall similarity in the shapes of the profiles. One rabbit suckled her young immediately after giving birth. Plasma levels increased during nursing.

considerable variation in the maximal levels of oxytocin measured in different animals but the mean interval between delivery of individual kittens was related to peak levels of hormone (Fig. 5). No temporal relationship between separate peaks of hormone and delivery of individual fetuses was demonstrated. It is possible that limitations of the assay procedure and speed of sampling tended to flatten out any pulses of hormone released into the circulation, so analysis of variance between the samples collected before and during birth were carried out, to see whether there was any greater fluctuation in oxytocin levels during delivery. An 'F' test gave significantly ($P < 0{\cdot}001$) higher values of variance in oxytocin levels in birth compared with pre-partum values and control experiments on days 28 and 29 of gestation.

Simultaneous recording of neuronal activity and measurement of plasma oxytocin

Four experiments were carried out in which it was possible to record neurone activity and monitor plasma oxytocin levels simultaneously. One of these neurones was classified as oxytocinergic on the basis of its pattern of discharge during birth

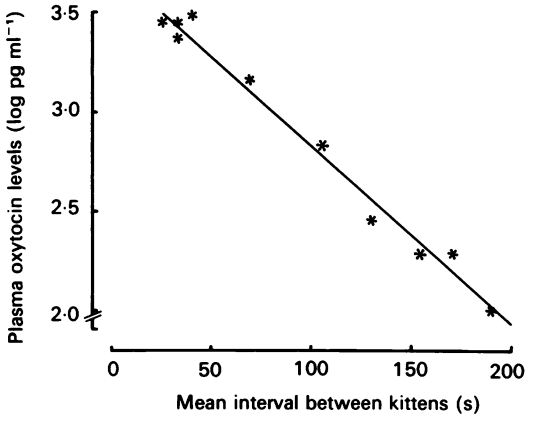

Fig. 5. The relationship between plasma oxytocin concentrations during delivery in the rabbit and the speed of delivery. Peak levels of plasma oxytocin observed in delivery in ten rabbits were plotted against the mean interval between delivery of individual fetuses for each animal (*). The best-fit time, fitted by the method of least squares, is shown (correlation co-efficient 0·99).

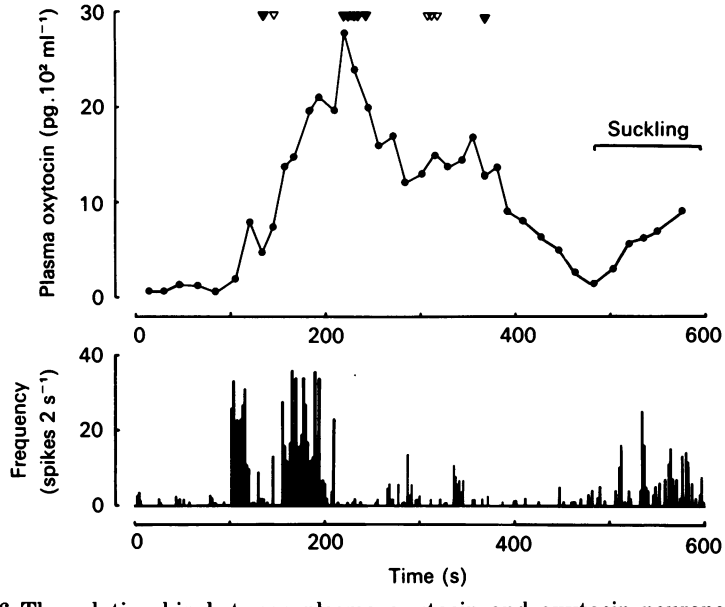

Fig. 6 The relationship between plasma oxytocin and oxytocin neurone activity in a conscious rabbit during delivery. Delivery of fetuses (▲) and placentae (△) are shown above the hormone profile. Note: (1) the onset of bursting discharge, typical of the activity of an oxytocin in birth, starts approximately 20 s before plasma oxytocin levels start to rise; (2) delivery of the first kitten followed 12 s later; (3) delivery of the first kitten follows the first peak of hormone, and delivery of several kittens in quick succession occurs after the second peak.

and the data are shown in Fig. 6. The onset of the bursting pattern of discharge preceded the rise in plasma oxytocin by 20 s and this, in turn, occurred before delivery of the first kitten.

Control experiments

Plasma oxytocin levels were measured in three rabbits (days 28–29 of gestation). Circulating levels of hormone were low ($15{\cdot}1 \pm 2{\cdot}5$ pg ml^{-1}) but still above base line levels of the assay. There was no statistically significantly greater degree of variance between plasma oxytocin in late gestation compared with plasma oxytocin immediately pre-partum, but mean plasma oxytocin was significantly ($P < 0{\cdot}02$; Student's t test) lower in late gestation. Haemorrhage did not induce the release of assayable oxytocin.

DISCUSSION

We set out to record the extracellular activity of oxytocin neurones during labour in the rabbit in an attempt to resolve the controversy about the role of oxytocin in birth. The activity of nineteen magnocellular neurones was compared with the discharge of sixteen neurones from the lateral hypothalamic area. Approximately half the magnocellular (8/19) showed an intermittent bursting discharge associated with reflex milk-ejection, a pattern of activity which is typical of oxytocin neurones in lactation (Paisley & Summerlee, 1984). In contrast, the remaining neurones (11/19) showed statistically significant falls in their firing rate during suckling which is characteristic of vasopressin neurones. The putative oxytocin neurones also showed a distinct pattern of discharge in labour with five to fourteen discrete bursts of high-frequency activity. Furthermore, each burst of discharge was temporally related to delivery of a fetus. Again in contrast to the oxytocin neurones, the vasopressin cells showed a decrease in their firing rate throughout delivery, which served to accentuate the different responses of the two populations of cells. The electrophysiological data imply that birth in the rabbit should be accompanied by a substantial rise in plasma oxytocin, which was shown to be true in experiments where plasma oxytocin was measured, and a fall, or at least no change, in plasma vasopressin levels. There are no recent data published to confirm this second point, but work by Haldar (1970), using a bioassay for vasopressin, suggested that there is a selective release of oxytocin and not vasopressin during labour in the rabbit. Low levels of vasopressin during delivery in the rabbit are anomalous compared with the increases in circulating vasopressin seen in other species; for example, the rat (Fuchs & Saito, 1971). However, Summerlee (1981) reported a significant increase in the firing rate of the putative vasopressin neurones in the conscious rat during birth, which supports the assay data in this species and highlights one of the differences between the activation of the magnocellular neurones in birth between the rat and the rabbit. This difference may represent the degree of stress engendered by the length of the expulsive phase of labour in the rat compared with the relatively short expulsive phase of birth in the rabbit.

The electrophysiological data imply that oxytocin is released into the circulation in pulses and that these drive synchronized myometrial activity to expel the

individual fetuses. However, pulsatile output of oxytocin could not be detected in the plasma samples taken during labour. A statistically significant greater degree of variance of the oxytocin titres was found in plasma samples collected in delivery which implies that the release was pulsatile but not detected for technical reasons. Labour in the rabbit is rapid (an average of seven kittens expelled in 7 min) and with the half-life of oxytocin 1·6–8·5 min (Ginsburg & Brown, 1956; Ginsburg, 1968) sampling every 10–15 s may not be sufficiently fast to detect discrete pulses of hormone released approximately once a minute. Perhaps the 'spurt-like' release of hormone observed in human labour (Gibbens & Chard, 1976; Otsuki, Yamaji, Fujita, Takagi & Tanizawa, 1983) reflects a longer interval between pulses of hormone released into the circulation by women in delivery. Other factors, such as the transfer of oxytocin from the site of release across the extracellular space and passage into the circulation, the mechanics of sampling or the presence of an active plasma oxytocinase, might also act to obscure a detectable pulsatile release.

There is only one other report concerning the levels of oxytocin, measured by radioimmunoassay, during delivery in rabbits (Fuchs & Dawood, 1980). It is difficult to compare the profiles we obtained with their data because the sampling and assay techniques employed were different. Fuchs & Dawood (1980) measured oxytocin in samples extracted from 5 ml of blood which could only be collected intermittently throughout delivery (approximately once every 5 min). There are some findings that are in common with both sets of experiments *and* some notable differences. We agree with Fuchs & Dawood (1980) that plasma oxytocin titres are in the range 50–100 pg ml^{-1} pre-partum and highest at the time of delivery of the first or second fetus, but the degree of change between the concentrations pre-partum and peak values during delivery are very different in the two sets of experiments: Fuchs & Dawood (1980) reported peak levels of 258 ± 89 pg ml^{-1} (mean $\pm$S.E.) whereas peak levels in our study were 2846 ± 326 pg ml^{-1}. Furthermore, Fuchs & Dawood (1980) suggested that there are pulses of oxytocin released in the immediate pre-partum period: a finding that was not substantiated in our experiments. Low levels of oxytocin were detected in our rabbits before birth and these titres were significantly greater than levels in the control periods on days 28–29 of gestation but the detailed profiles did not show any evidence of pulsatile release nor was there a statistically greater degree of variance among values in the immediate pre-partum period compared with the control experiments.

We succeeded in recording from one oxytocin neurone whilst chronically sampling the blood for oxytocin assay. Notwithstanding the paucity of simultaneous data, the relationships between the rise in plasma oxytocin and delivery of the first fetus and the onset of the bursting activity from oxytocin neurones and delivery described in our experiments are relativity constant and imply that oxytocin neurone activation is followed by a rise in plasma oxytocin which, in turn, is followed by delivery. These temporal relationships were confirmed in the simultaneous experiment (Fig. 6) and indicate that the Ferguson reflex (Ferguson, 1941) is operational. The passage of the fetus through the cervix and into the birth canal provokes a reflex activation of oxytocin neurones. This generates a pulsatile release of oxytocin from the neurohypophysis, thereby boosting and maintaining circulating levels of hormone. It is conceivable that neurosecretory activation could be the principal driving force in

delivery. Pulsatile release of oxytocin might cause greater contractile effort from the myometrium which squeezes the fetus into the birth canal but this is unlikely for two reasons: (1) distension of the birth canal, in anaesthetized rats, stimulated increased magnocellular neurone discharge (Dreifuss, Tribollet & Baertschi, 1976) so it is plausible that each fetus might cause reflex activation of the oxytocin neurones; (2) no definite relationship between pulses of oxytocin and delivery of fetuses was demonstrated whereas there was a marked relationship between neurosecretory activation and delivery. Although it seems likely that oxytocin is released in a pulsatile manner, it is not the pulsatility which is the key to delivery. Spinal cord section (Fuchs & Dawood, 1980) and epidural analgesia (Flint, Forsling & Mitchell, 1978) which would block transmission of the sensory information from the birth canal, and hence reflex activation of the oxytocin neurones do not disrupt the overall pattern of delivery, which again suggest that pulsatile release of oxytocin is not the primary driving force in birth. However, oxytocin concentrations are important for the efficiency of labour in the rabbit. We have shown that peak oxytocin levels are directly related to the speed of delivery and a similar correlation has been demonstrated between peak oxytocin concentrations and the electrical activity of the myometrium in the miniature pig (M.A.M. Taverne, cited by Forsling, MacDonald & Ellendorff, 1979).

Our experiments show that oxytocin neurones in the rabbit display bursts of electrical activity related to delivery similar to the activity of oxytocin neurones in the rat during delivery (Summerlee, 1981). There are some differences in the pattern of discharge of magnocellular neurones in the rabbit: (1) oxytocin neurones only give bursts of activity related to delivery of a fetus but not to abdominal contractions nor delivery of placental material as reported for the rat; (2) the bursts of discharge during birth in the rabbit are very prolonged and composed of a series of smaller bursts of even higher frequency discharge; and (3) vasopressin neurones in the rabbit show a fall in their rate of discharge, confirming bioassay data that vasopressin is not released in labour in the rabbit. Our results also report for the first time simultaneous recordings of oxytocin neurone activity whilst chronically sampling the blood for plasma oxytocin assay in the same animal and confirm that changes in neuronal discharge are followed by changes in circulating levels of hormone, which in turn are followed by delivery.

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