EFFECTS OF ELECTRICAL STIMULATION OF THE NEUROHYPOPHYSIS ON LABOUR IN THE RAT

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SUMMARY

Labour was studied in 69 primiparous and multiparous rats by continuous observation and by the recording of intra-uterine activity. The effect of electrical stimulation of the neurohypophysis with stimulation parameters selected to create a pulsatile release of oxytocin was investigated. Stimulation was applied to the neurohypophysis through chronically implanted electrodes every 5 min, in 45 min sessions, from noon on Day 21 of gestation and at 3 h intervals thereafter.

Electrical stimulation successfully promoted (or induced) the onset and facilitated the course of labour. Stimulation at 12.00 h on Day 21, or at a subsequent stimulation session 3, 6, 9 or more hours later, promoted an immediate increase in the frequency and amplitude of uterine contractions. Overt signs of abdominal straining followed within 5–30 min and the first pup was delivered shortly thereafter. These 'induced' deliveries were almost identical to those displayed by control rats; labour continued to completion despite the termination of the stimulation session after 45 min. By contrast, one third of the stimulated animals displayed an interrupted pattern of labour in which events virtually ceased for 30–60 min when stimulation was terminated. Stimulation, however, only advanced labour by 1–2 h in relation to control animals; this was not statistically significant.

Stimulation accelerated the delivery of the first 5 pups in each litter. In both stimulated and control animals, the birth intervals declined over these first few deliveries to reach the lowest values of 5–6 min throughout the remainder of labour. The most common litter size was 12 pups.

The distribution of labour on Day 21 and 22 was bimodal. Seventy per cent of the animals gave birth between 12.00 and 18.00 h on Day 21, a few gave birth during the following night and the remainder formed a second peak on Day 22. All litters of less than 6 pups were born during this later period.

The implications of these results in the context of spontaneous labour are discussed. We conclude that endogenous oxytocin (with perhaps other neurohypophysial hormones) released in pulses of 1–3 mu. every 5 min can promote a pattern of labour on Day 21 of gestation that is almost indistinguishable from that which occurs naturally.

INTRODUCTION

Oxytocin has been found to induce 'normal' labour when administered in amounts that may be regarded as physiological. The hypothalamo-neurohypophysial system (HNS) is the site of oxytocin production and this appears, from several different experimental approaches, to be activated in both the mother and foetus during labour (Swaab & Jongkind, 1970;

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Chard, 1973). The activation of the HNS of the foetus probably relates to stress, and there is no evidence at the present time to indicate that this foetal oxytocin influences the time of birth (Honnebier & Swaab, 1973; Swaab & Honnebier, 1973, 1974). Many studies have detected oxytocin in the peripheral plasma of the mother in labour, and the recorded levels have tended to be highest during the terminal stages of delivery (Chard, 1972). Despite this appearance of oxytocin in the blood and the knowledge that it can promote uterine activity, the exact role of oxytocin in natural labour remains unsettled.

A sudden activation of the HNS by a neural or neurohumoral stimulus could release a surge of oxytocin and precipitate the sudden onset of labour with the rapid delivery of the young. Such a development could account for the explosive pattern of delivery observed in species such as the rabbit where the full litter is usually delivered in less than 10 min (Fuchs, 1964). Furthermore, a normal labour can be promoted in the rabbit by either the injection of 100 mu. oxytocin (Cross, 1958; Fuchs, 1964) or the release of endogenous oxytocin through 10 s of electrical stimulation applied to the HNS (Lincoln, 1971). These methods can advance labour in the rabbit by 24–72 h.

Clearly not all species deliver their young with such rapidity. The labour of the rat lasts for 1–2 h, and in contrast to the rabbit this has only successfully been induced by the prolonged i.v. infusion of oxytocin at 2 mu./min (Fuchs & Poblete, 1970). Such infusions involve the administration of 100 mu. oxytocin or more. This is an unphysiologically large amount of hormone and at best labour is only advanced by 4–5 h. How could endogenous oxytocin be involved in the labour of a species such as the rat? A continuous release of oxytocin throughout labour is unlikely, for the oxytocinergic neurones of the HNS have to accelerate to over 30 action potentials/s to release a significant amount of oxytocin (1–2 mu.), and these rates can only be sustained for a few seconds at a time (Lincoln & Wakerley, 1974). Two possibilities do exist, oxytocin may be released as a pulse every few minutes throughout labour, as occurs during suckling (Lincoln, Hill & Wakerley, 1973). Alternatively, oxytocin may be released during the terminal stages of delivery in response to the dilatation of the birth canal (Ferguson, 1941).

In the present studies we have attempted to determine whether endogenous oxytocin (and possibly other neurohypophysial hormones) could be made to induce labour in the rat when released by periodic electrical stimulation of the neurohypophysis.

MATERIALS AND METHODS

Sixty-nine female rats of a Wistar strain, weighing 200–300 g, were used, excluding those which died as a result of surgery. Data from 16 primiparous rats forming the control of a previous study were included in Fig. 7 (Boer, Boer & Swaab, 1974). Daily illumination was provided from 07.00 to 19.00 h, and food and water were available *ad libitum*. Vaginal smears were taken daily between 08.00 and 10.00 h. Day 0 of pregnancy was assigned to the day on which spermatozoa were found in the vaginal smear.

Implantation of electrodes

Concentric bipolar electrodes for the stimulation of the neurohypophysis were prepared from diamel-insulated platinum wire (0.2 mm) and stainless steel tubing (0.6 mm outer diameter) insulated with varnish. The tip of each electrode was sharpened to a conical point by grinding against a whetstone.

The animals were anaesthetized with 6 mg sodium pentobarbitone (Nembutal, Abbott Laboratories), and supplementary ether was given when the barbiturate anaesthesia proved inadequate for the placement of the animal into the stereotaxic headholder. The electrodes

were implanted into the neurohypophysis from a midline dorsal approach using pre-determined stereotaxic co-ordinates, and the electrodes were secured to the skull by four screws and dental acrylic. The mortality from this operation was high (about 60 %), but all surviving animals appeared perfectly healthy. They displayed no signs of diabetes insipidus and reared their young. Electrodes were successfully implanted into 23 primiparous rats on Day 15 of pregnancy (Series 1), and into 17 multiparous rats at least 1 week before the onset of pregnancy (Series 2).

Implantation of radio-pills

Pressure-sensitive radio-pills (Rigel Research Ltd) were implanted into seven animals on either Day 19 or 20 of gestation to record intra-uterine pressure changes during labour. The animals were anaesthetized with ether and the uterus was exposed through an abdominal incision. The foetus closest to the ovarian end of one of the uterine horns was removed through a small incision, and a radio-pill about equal in size to that of a 20-day foetus was inserted with the pressure-sensitive surface directed down the uterus towards the adjacent foetus. The distal end of the pill was ligated to the upper end of the uterine horn. The placenta of the displaced foetus was usually left *in situ*. Haemorrhage was minimal.

Electrical stimulation of the neurohypophysis

Both series of animals were non-selectively divided into stimulated and control (sham-stimulated) groups. In series 1, 15 animals were electrically stimulated according to the procedure given below and eight served as controls. In series 2, 11 stimulated and six control rats were used. These animals were all transferred to the laboratory on Day 20 of gestation or earlier, and watched continuously from 09.00 h on Day 21 until delivery occurred. Red light was used for observation between 19.00 and 07.00 h.

Each stimulation session lasted for 45 min and consisted of 10 stimulus trains of 10 s each, spaced at 5 min intervals. Stimulation or sham-stimulation commenced at 12.00 h on Day 21 and was repeated every 3 h until labour had occurred. Stimulation was applied in the form of 800 μ A biphasic block pulses each of 2 ms duration at 60 Hz. When an animal displayed an overt response to stimulation the current was lowered to 600 or 400 μ A. The pulse parameters were provided from a Grass stimulator (Model S8) with stimulus isolation; the current was monitored continuously.

The effectiveness of each electrode in the release of neurohypophysial hormones was tested 9–14 days after parturition by examining the milk-ejection response promoted by electrical stimulation. The current threshold for milk ejection was measured in all animals, and in some animals more precise measurements were made by comparing the rise in intra-mammary pressure promoted by stimulation with that elicited by known amounts of oxytocin injected into the great saphenous vein (for techniques see Lincoln, Boer & Swaab, 1974).

Registration and calculation of data

The events of labour and the associated maternal behaviour were recorded by continuous observation. Uterine contractions and intramammary pressures were transmitted from the telemetry pills to an FM radio receiver (Rigel Research) and plotted on a flat deck recorder (Servogor-S).

Gestation length was calculated to the minute, from the onset of Day 0 until delivery of the first pup. The delivery of the first pup was regarded as the onset of parturition. The duration of parturition was the time from the delivery of the first to the last pup of a litter. The birth interval was the time between the deliveries of successive pups.

RESULTS

Intra-uterine pressure recordings during labour

The course of spontaneous labour in animals with intra-uterine pressure pills was for the most part similar to that observed in unoperated animals. The first contractions were usually recorded some hours before the delivery of the first pup, and the contractions tended to occur in groups lasting some minutes at a time. The frequency of such groups and the intensity of these contractions gradually increased until they finally merged into a period of continuous contractile activity commencing some minutes before the expulsion of the first pup. These final contractions were of large amplitude and were often associated with a rise in residual pressure (Fig. 1). Large, but brief, pressure spikes caused by abdominal straining motions appeared superimposed on the intrinsic uterine activity, and a number of such contractions preceded the delivery of each pup or placenta. Uterine activity decreased sharply after the delivery of the last pup (or placenta) and pressure peaks negative in relation to the baseline sometimes appeared (Fig. 1).

Fig. 1. A recording of intra-uterine pressure from a rat during natural labour on Day 21 of gestation, obtained from an implanted pressure-sensitive radio-pill. Tracings (a), (b) and (c) form a continuous recording. The numbers in (b) indicate the deliveries of both pups and placentae, except for the placentae (P) of pups 5, 6, 7 and 11 which were expelled sometime after the young. The recording shown in (d) was obtained 8 h *post partum*. The horizontal lines indicate the margins of the recording paper. The spikes superimposed upon some of the largest uterine contractions were caused by abdominal straining. Note, the burst-like configuration of the contractions before the expulsion phase of labour, and the appearance of negative pressure waves after the expulsion of the last pup.

Electrical stimulation of the neurohypophysis for 10 s, in the hours immediately before delivery, elicited uterine contractions lasting for a total of 10–15 min (Fig. 2). When stimulation was repeated at intervals of 3–5 min, a longer period of contractile activity developed comparable to that observed during spontaneous labour. Stimulation applied immediately *post partum* also induced an increase in uterine activity, but the induced pressure waves were of lower amplitude and frequency (Fig. 2). In all these situations the

results of 10 s of electrical stimulation were easily reproduced by the injection into the great saphenous vein of oxytocin in amounts up to 2 mu.

As a result of the studies mentioned above, a stimulation programme was evolved for the evaluation of labour in which stimulation was applied every 5 min in 45 min sessions commencing at 12.00 h on Day 21; these sessions were then repeated every 3 h until labour had occurred (see Methods). The effect of this stimulation programme on the course of labour was also investigated in animals with intra-uterine pressure pills but the data were not included in the calculations which follow.

Fig. 2. Effect of electrical stimulation of the neurohypophysis and of oxytocin administration on the contractile activity of the pre- and post-partum rat uterus. The pre-partum recordings were made on Day 22 in an animal displaying a protracted pregnancy. Each vertical event mark represents a 10 s train of stimuli, the parameters of which are shown lower right. Oxytocin was administered via a cannula inserted through the great saphenous vein. Note: (1) a single train of 10 s stimulation evoked in the pre-partum situation 10–15 min of increased uterine activity, and was mimicked by 2 mu. oxytocin; (2) the increase in baseline pressure, particularly when the pre-partum situation stimulation was applied at intervals of 3–4 min; (3) the lower frequency of contractions in the post-partum period.

The effects of repeated stimulation of the neurohypophysis of an animal on the afternoon of Day 21 is illustrated by the uterine contractions depicted in Fig. 3. In this animal, and in others stimulated close to term, contractions commenced almost immediately after the first 10 s of stimulation, or when contractile activity was already in progress the amplitude and frequency of the contractions increased. Abdominal straining was observed within 5 min in the recording illustrated and the first pup was delivered 23 min after the stimulation session commenced. Uterine activity continued after the stimulation session terminated at 45 min, but the course of events slowed and contractions decreased in frequency and amplitude. Note the tendency for contractions in the post-stimulation period to be grouped into bursts. When the next stimulation session commenced (3 h after the first), contractions soon increased in amplitude and the seventh and last pup was expelled. Changes in baseline pressure were observed but these were not consistent from one animal to another.

Fig. 3. A recording of intra-uterine pressure from a rat on Day 21 of gestation during the induction of labour by electrical stimulation of the neurohypophysis. Tracings (a), (b), (c) and (d) form a continuous recording. Each vertical event mark indicates a single train of 10 s stimulation, the parameters of which are given in Fig. 2. The numbers indicate the deliveries of both pups and placentae, except for the placentae (P) of pups 6 and 7 which were delivered some time after the young were born. The horizontal lines indicate the margins of the recording paper, adjustments to which were necessary to encompass the changes in baseline pressure encountered over the 4 h of recording shown. Trace (e) represents the uterine pressure response to a single train of stimuli applied 2 h after the delivery of the seventh and last foetus. Note: (1) the appearance of uterine contractions after the onset of stimulation in both tracings (a) and (c), (2) the development of bursts of contractile activity between the two stimulation sessions; (3) the decline in uterine contractions and the disappearance of abdominal contraction spikes after delivery of the last placenta despite the application of further stimulation trains.

Delivery patterns after neurohypophysial stimulation

Eight representative patterns of labour in control animals, recording the overt signs of labour and the delivery of the pups against time, are shown in Fig. 4. These control animals carried implanted stimulation electrodes, but stimulation was never applied. The pre-delivery phase of lordosis-type abdominal straining varied considerably in length, and was of longer duration and more pronounced in primiparous than multiparous animals. It was not uncommon, with the latter, for the first outward sign of labour to be the actual expulsion of the first pup.

The delivery of the young in the electrically stimulated group followed a similar pattern to that observed in the control animals, with the exception that labour was time-locked within broad limits to the onset of stimulation (Fig. 5). Thus, in Fig. 5a are shown eight 'classic' (i.e. non-interrupted) patterns of labour in animals after stimulation at times from

12.00 to 21.00 h on Day 21. It should be remembered that animals which started labour after stimulation at, for example, 21.00 h had already received stimulation at 12.00, 15.00 and 18.00 h without effect. The patterns of deliveries shown in Fig. 5a are almost indistinguishable from those of control rats, and in all cases labour continued after the 45 min stimulation session terminated. By contrast, one third of the primiparous rats and the majority of the pill-implanted animals displayed an interrupted pattern of labour after stimulation (Fig. 5b). With these animals labour seemed to enter a period of arrest when the stimulation session ceased, but it was temporary and vigorous labour usually developed well before the next stimulation session was due. Occasionally a parallel phenomenon was observed in which stimulation promoted lordosis-type abdominal straining without the delivery of young. In most of these cases a normal pattern of labour was observed after the subsequent period of stimulation.

Fig. 4. Patterns of parturition in control rats. Eight representative delivery patterns are shown, synchronized to the time at which the first pup was delivered. The time (h) of this first delivery on Day 21 is shown on the left. Each arrow indicates the expulsion of a single pup. Shaded areas, periods of abdominal straining before delivery of the first pup.

The onset of abdominal straining was closely correlated with the onset of one of the stimulation sessions, though abdominal straining was difficult to quantify and time. The delivery of the first pup was a precise event, but this sometimes did not occur until an hour or more after the development of overt signs of straining. Despite these variations, the time of the first delivery was significantly correlated with stimulation. Thus, control rats delivered their first young at random in relation to sham-stimulation, whilst electrically stimulated rats mostly delivered their first young within 90 min of the onset of a stimulation session ($P = 0.01$) (Fig. 6).

Length of gestation

The mean length of gestation of primiparous control animals was 526 h 8 min $\pm$ 180 (S.E.M.) min ($n = 8$), and stimulated animals 525 h 14 min $\pm$ 143 min ($n = 14$). Gestation was timed from midnight, between the day of pro-oestrus and oestrus. With the multiparous rats the lengths of gestation of control and stimulated animals were 520 h 42 min $\pm$ 163 min ($n = 6$)

Fig. 5. Induction of labour in rats by electrical stimulation of the neurohypophysis. Each stimulation train is indicated by a vertical event mark placed both above and below the figure, there being 10 such stimulus trains in each stimulation session. The time (h) at which stimulation was given on Day 21, and from which labour resulted, is given to the left of the figure. The arrows indicate the delivery of individual young and the hatched areas represent the periods of abdominal straining before the first delivery. The broad arrow indicates the time in this particular animal at which the subsequent period of stimulation was commenced – the first period of stimulation having inadvertently been delayed by 20 min. The asterisks signify multiparous animals. Two types of labour were observed. (a) 'Classical patterns', in which labour resembled the pattern displayed by control animals. (b) 'Interrupted patterns', characterized by one or more prolonged birth intervals after the removal of the intermittent stimulus at 45 min.

and 522 h 11 min $\pm$ 172 min ($n = 9$), respectively. These mean values, however, have limited application for the distributions were not statistically normal. Figure 7 illustrates that 70 % of the labours of both control and stimulated rats (i.e. 41 animals) commenced between 12.00 and 18.00 h on Day 21, with only two animals delivering before noon. Few animals then delivered during the hours of darkness, so creating a second but smaller peak on Day 22. Thus, the mean time for the delivery of the first pup in all animals of 20.04 h on Day 21 corresponded to a time when the occurrence of a delivery was most unlikely.

The median length of gestation of primiparous control rats was 522 h 33 min and of stimulated animals 520 h 28 min. The corresponding figures for the multiparous animals

Fig. 6. Effect of stimulation (■) and sham-stimulation (▨) on the time of the first delivery. The 3 h interval, between one stimulation or sham-stimulation session and the next, in which the first delivery occurred has been divided into two for this analysis. Note the onset of labour, as defined by the delivery of the first pup, was random in the sham-stimulated group and equal numbers of rats delivered their first pup in each 90 min period. By contrast, the majority of the stimulated rats delivered their first pup within 90 min of stimulation; the distribution was significantly different from that observed in the sham-stimulated control animals ($P = 0.01$). □, Primiparous rats; ▨, multiparous rats.

Fig. 7. A histogram showing the time of the first delivery on Days 21 and 22 of gestation in stimulated (■), sham-stimulated (▨) and unoperated (□) rats. The photoperiod is given at the top of the figure with darkness represented by the thick bar. Note, the incidence of labour increased abruptly at about noon on Day 21, but the distribution was bimodal due to a proportion of animals delivering on Day 22.

were 518 h 45 min and 518 h 8 min, respectively. When these were combined the median time of all the control animals was 17.17 h on Day 21 and of stimulated animals 15.43 h.

Length of gestation was related to litter size, all litters containing less than 6 pups were delivered on Day 22. The most common litter size was 12 pups.

Duration of labour

There was no statistically significant difference between the duration of labour in control and electrically stimulated rats, when labour was measured from the delivery of the first to the last pup. The duration of labour in the primiparous group was 82 ± 16 min and in the

Fig. 8. (a) Distribution of birth intervals (min) in stimulated (...) and control (—) rats. Note the tendency for the stimulated animals to display shorter birth intervals. (b) Mean duration (min) of each birth interval throughout the litter. Five abnormally long birth intervals (> 50 min) have been excluded (see text). The linear regression lines have been calculated separately for the stimulation ($\blacklozenge$) and control ($\circ$) groups for the first four birth intervals, thereafter both groups have been combined and a single regression calculated.

stimulated group 88 ± 12 min; the corresponding figures for the multiparous animals were 114 ± 26 min and 74 ± 3 min. These mean figures conceal some rather interesting facts for whilst stimulation produced a number of prolonged (interrupted) labours stimulation would also appear to have hastened the delivery of others. The most common birth interval between the delivery of one pup and the next was 5–6 min (Fig. 8a), but the distribution was skewed and a few intervals exceeded 50 min. Figure 8b shows that the birth interval decreased in both control and stimulated animals from the delivery of the first to the fifth pup, thereafter the birth interval remained rather uniform. In the presentation of Fig. 8b, five abnormally long birth intervals (> 50 min) have been excluded, with one exception these long birth intervals were from stimulated animals displaying an interrupted pattern of labour. Allowing for this exercise, it can be seen from Fig. 8b that the first four birth intervals in the stimulated group were substantially shorter than those observed in control animals, indicating that the early part of the delivery phase proceeded with more rapidity in stimulated than in control animals. This has been confirmed statistically, for when the abnormally long intervals are returned and the data compared by a non-parametric test the first four birth intervals in the stimulated group are significantly shorter ($P = 0.05$).

Control of electrode localization

Three of the 26 animals in the stimulation groups were not found to display a release of oxytocin when the same stimulation parameters were applied during lactation; the release of oxytocin being assessed by the observation of a milk-ejection response from the suckling young (see Methods). The results of these three animals were therefore excluded. With 17 of the remainder, milk ejection was observed after application of a 10 s period of stimulation at 60 Hz with currents of 300 μA or less, a substantially smaller current than was normally applied during the induction of labour. The oxytocin-threshold for the triggering of a milk-ejection response from the suckling young is 0.2–0.4 mu. (Lincoln, 1973). An intramammary pressure recording from a rat at Day 10 of lactation is shown in Fig. 9. Here, in the same rat, the effect of electrical stimulation of the neurohypophysis was compared with the effect of oxytocin injected into the great saphenous vein. From observations such as those reported in Fig. 9, we conclude that each 10 s burst of stimulation applied during labour released 1–3 mu. oxytocin.

Fig. 9. Intramammary pressure recordings from a rat in mid-lactation, after an electrically induced labour, illustrating the effect of electrical stimulation and the i.v. injection of synthetic oxytocin. (a) The effect of oxytocin alone, amount being given is in mu. 'F' indicates the flushing of the cannula in the change from one concentration of hormone to another. Note the short duration of each pressure wave in relation to those displayed by the uterus (Fig. 2). (b) The effect of electrical stimulation of the neurohypophysis alternating with control injections of oxytocin. Note the stimulation threshold between 100 and 150 μA , and compare the pressure response promoted by stimulation with that elicited with exogenous oxytocin.

DISCUSSION

Although oxytocin can be made to induce labour in the rat when administered by a prolonged infusion in very late gestation (Fuchs & Poblete, 1970), it is difficult to determine from such evidence whether endogenous oxytocin promotes or facilitates the natural labour of this species. We have sought a more definitive approach by electrically stimulating the release of the animal's own neurohypophysial stores of oxytocin. This was not without its problems; continuous stimulation does not mimic an infusion for hormone release soon falls to unmeasurable values. Secondly, current electrophysiological evidence suggests that the oxytocinergic neurones of the HNS may only be able to fire at the rates required for oxytocin release (> 30 action potentials/s) for a few seconds at a time (Lincoln & Wakerley, 1974). A single injection of oxytocin does not induce labour in the rat (Fuchs & Poblete, 1970), and likewise we found a single period of 10 s stimulation to be without effect though it would promote up to 10 min of increased uterine activity. Thus, a stimulation protocol was

constructed with the objective of releasing a pulse of oxytocin every 5 min for a 45 min period, thereby we hoped that the uterine activity promoted by one pulse of oxytocin would be supported by the next and so on. Such a pulsatile release has a physiological parallel in the release of oxytocin by the rat during nursing; here uniform pulses of 0.5–1.5 mu. oxytocin are released every 5–15 min during each period of continuous suckling by the young (Wakerley & Lincoln, 1971; Lincoln *et al.* 1973). Each pulse of oxytocin in this situation is precipitated by a stereotyped 2–4 s acceleration in the firing of half the neurones (the oxytocinergic neurones) in the paraventricular (Wakerley & Lincoln, 1973) and supraoptic nuclei (Lincoln & Wakerley, 1974). The observation of bursts of contractile activity during the onset of spontaneous labour suggests that a pulsatile release of oxytocin might be occurring. In man a pulsatile release of oxytocin has been reported with the pulses increasing in frequency near to the expulsion of the foetus (Gibbens, Boyd & Chard, 1972).

Whilst we have employed stimulation parameters known to release oxytocin both *in vivo* (Cross & Harris, 1952; Harris, Manabe & Ruf, 1969) and *in vitro* (Ishida, 1970; Dreifuss, Kalnins, Kelly & Ruf, 1971), such stimulation undoubtedly releases other neurohypophysial peptides such as vasopressin (Douglas & Poisner, 1964). This second hormone is also released in labour (Fuchs & Saito, 1971), and thus one could argue that the dual release of both hormones by stimulation approximates more closely to what may occur naturally.

A single train of stimuli applied to the neurohypophysis of the rat did not create the results observed in rabbits, in which a single 20 s burst of stimulation on Day 30 or 31 of gestation promoted the birth of the entire litter within the next 20 min (Lincoln, 1971). The rabbit uterus, however, is sensitive to the action of oxytocin for some 48 h before parturition, and when delivery does occur it is abrupt in onset and quickly completed. However, the rat uterus only develops any appreciable sensitivity to oxytocin within 6 h of delivery, and labour then lasts for 1–3 h (Fuchs, 1969).

The observation of parturient behaviour time-locked to stimulation, as assessed by observations of uterine activity, abdominal straining and the expulsion of the young, is strong evidence in support of the view that endogenous oxytocin can promote the delivery of the young when released close to term. Two other pieces of evidence also give support to this view. The observation that labour ceased, at least for a period of 30–60 min, when stimulation was terminated in some animals suggests that the continuation of labour was dependent on the further support provided by endogenous oxytocin. Secondly, stimulation shortened the birth interval between the delivery of the first few pups in the litter, i.e. stimulation accelerated events. The mean duration of labour was not significantly shortened by stimulation for the increase in the speed with which the first few pups were born was balanced by the long labours of those animals displaying an interrupted pattern of delivery. When the abnormally long birth intervals of this latter group are replaced by intervals representing the average birth interval observed in control animals (9.4 min) then the mean duration of labour in the stimulated animals is 15.8 min shorter than that observed in control animals (66.2 min compared with 82.0 min).

The stimulated animals gave birth earlier on Day 21 than the control animals, but the advance in the time of labour was small and not significant. This lack of significance was caused by the fact that there was considerable variation in the time at which labour occurred relative to the comparatively small period of time over which the uterus developed its apparent sensitivity to oxytocin. Stimulation at 12.00 h on Day 21 was often without effect, though a normal labour often followed stimulation 3 h later. The interrupted pattern of labour would appear to represent a 'half-way house' in which the factors governing uterine activity were insufficient to support labour when stimulation was removed, though it should be recalled that labour usually restarted within 60 min without further experimental assistance. Thus, the neurohypophysial-uterine system would appear to change in 3 h or

less from a situation where neurohypophysial hormones are ineffective in the support of labour to a state where they can facilitate and promote events.

Other studies have already shown that most deliveries in rats occur during the period of light, i.e. the period of rest in this species (Naaktgeboren & Slijper, 1970; Mitchell & Yochim, 1970), and our findings of a distribution pattern dependent on length of gestation as well as the light:darkness cycle conform with the idea that several systems are involved in the induction of labour. The distribution of labours showed a very abrupt rise in the early afternoon of Day 21 with a second smaller and broader peak on Day 22. There was not a time displacement of 24 h between these peaks, but it was clear from observations of behaviour that once the lights went out at 19.00 h on Day 21 the rats 'lost all interest in giving birth'.

The present study supports the concept that neurohypophysial hormones of endogenous origin can promote or facilitate labour in the rat, and confirms that the changes in the uterine response to these hormones is most rapid in the hours immediately before delivery. These studies do not prove that oxytocin is released during natural labour in the pulsatile manner created by stimulation; we need to develop an on-line assay whereby we can monitor the second-by-second release of neurohypophysial hormones during natural labour. We assume in our discussion that oxytocin plays an essential role in normal labour, but this assumption remains both difficult to support or refute for other unknown neurohypophysial substances might be involved.

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