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Changes in immunostaining for oxytocin in the forebrain of the female rat during late pregnancy, parturition and early lactation

G.F. Jirikowski[1], J.D. Caldwell[2], Ch. Pilgrim[1], W.E. Stumpf[3], and C.A. Pedersen[2]

[1] Abteilung Anatomie und Zellbiologie, Universität Ulm, Federal Republic of Germany;
[2] Biological Sciences Research Center and [3] Department of Anatomy, University of North Carolina, Chapel Hill, North Carolina, USA

Summary. Serial brain sections of female rats at late pregnancy, parturition or early lactation were immunostained for oxytocin. Immunoreactive perikarya were visible in the magnocellular nuclei in all experimental animals as well as in ovariectomized, nulliparous controls. During late pregnancy and at parturition additional immunostaining appeared in groups of perivascular neurons in the preoptic region, the lateral subcommissural nucleus, the perifornical region and scattered throughout the ventral portion of the hypothalamus. Immunostaining of almost all of these perivascular neurons disappeared by day two postpartum, while another population of oxytocin neurons, without association with blood vessels, appeared in these brain regions after parturition. Immunostaining of processes from oxytocinergic neurons in the periventricular nucleus increased markedly near parturition. Many of these processes projected toward the third ventricle. Oxytocinergic neuronal systems that are activated in late pregnancy and early postpartum may contribute to several physiological changes associated with parturition and lactation including the onset of maternal behavior.

Key words: Oxytocin – Hypothalamus – Pregnancy – Parturition – Lactation – Rat (Wistar)

Oxytocin (OT)-producing neurons are located in the paraventricular (pvn) and supraoptic (son) nuclei of the hypothalamus and in various regions outside of the classical magnocellular nuclei, normally referred to as accessory nuclei (for review, see Fisher et al. 1979; Sofroniew 1985; Swanson and Kuypers 1980). Perivascular clusters of magnocellular neurons around larger blood vessels that connect the pvn and son have been described as intersupraopticoparaventricular islands (ispi) (Dawood 1984). In addition to contributing to the hypothalamo-neurohypophysial tract, processes from oxytocinergic neurons are distributed widely within the limbic system (Buijs and Swaab 1979), the brain stem and the spinal cord (Sofroniew and Schrell 1981). Oxytocin neurons with central projections have been reported to originate from the dorsocaudal portion of the pvn (Rhodes et al. 1981), from the anterior commissural nucleus (comparable to the area described in this paper as the lateral subcommissural nucleus lsn), the preoptic region (Scott et al. 1986), and from the zona incerta (Smithson and Hatton 1986).

Apart from the classical effects on milk ejection and labor, oxytocin may have a number of functions within the brain including the stimulation of sexual and maternal behavior (Pedersen et al. 1985; Fahrbach et al. 1985; Van Leengood et al. 1987; Arletti and Bertolini 1985; Caldwell et al. 1986).

Oxytocinergic neurons are influenced by ovarian steroids. Estrogen treatment increases electrical activity of oxytocin neurons (Akaishi and Sakuma 1985), stimulates the secretion of oxytocin into the portal and systemic circulation, and increases oxytocin binding in several brain regions (Sarkar and Gibbs 1984; Unger and Schwarzenberg 1970; Yamaguchi et al. 1979; DeKloet et al. 1985; Negoro et al. 1973). Some of the oxytocinergic neurons in the magnocellular nuclei have nuclear receptor sites for estradiol (Sar and Stumpf 1980; Rhodes et al. 1982; Jirikowski et al. 1987). Estrogen treatment alters the distribution of oxytocin-immunoreactive neurons in the brain (Rhodes et al. 1981; Jiriskowski et al. 1988). In late pregnancy oxytocin appears to mediate as a neurotransmitter oder neuromodulator the facilitating effect of ovarian steroids on the onset of maternal behavior (Pedersen et al. 1985; Fahrbach et al. 1985; Van Leengood et al. 1987).

The aim of the present study was to determine changes in the pattern of oxytocin immunostaining in the rat forebrain during late pregnancy, parturition and early lactation when dramatic changes in endogenous levels of ovarian steroids occur (Gerber 1979) and when maternal behavior emerges.

Materials and methods

We used timed pregnant female Wistar rats (Charles River Wiga GmbH., Sulzfeld FRG). Females were housed with sexually active males overnight. The day upon which sperm appeared in daily vaginal smears was considered to be day 0 of pregnancy. Animals were killed between 8 and 10 a.m. on day 15 or day 18 of pregnancy, at parturition (after delivery of four pups) or on days 2, 5 or 30 postpartum. Pups were removed from the mothers' cages on day 24 postpartum. Six animals were in each experimental group. In the control group, 6 nulliparous rats were killed two weeks after bilateral ovariectomy (OVX), Animals were anesthetized

Send offprint requests to: Dr. Gustav Jirikowski, Abteilung Anatomie und Zellbiologie, Universität Ulm, Postfach 4066, D-7900 Ulm, Federal Republic of Germany

with chloral hydrate (40 mg per 100 g bw in isotonic saline) and perfused through the heart with 1% paraformaldehyde in phosphate-buffered saline (PBS), pH 7.7 (PBS), for 15 min. Brains were removed and postfixed in 4% paraformaldehyde in PBS overnight. Serial frontal sections (50 μm) were cut on a Vibratome (Lancer).

Immunocytochemical procedures

Antisera to oxytocin were raised in rabbits by intradermal immunization with synthetic oxytocin coupled to thyroglobulin by paraformaldehyde. For details on the preparation and characterization of the antisera, see Jirikowski et al. (1988). Vibratome sections were incubated overnight in oxytocin-antiserum diluted 1:5000 in PBS containing 0.05% Triton X 100 at 4° C. The primary antibody was used preabsorbed with synthetic arg-vasopressin (100 μg/ml) and synthetic arg-vasotocin (100 μg/ml, both peptides obtained from Sigma). Immunoprecipitates were visualized with the peroxidase-anti-peroxidase method. Anti-rabbit IgG and rabbit peroxidase-antiperoxidase complex were obtained from DACO (Hamburg, FRG). The reaction product was stained with 3′3′diaminobenzidine and hydrogen peroxide. Stained sections were rinsed in water, mounted with Entellan and examined with a Zeiss photomicroscope. Sections of additional animals were used for immunocytochemical controls with the primary antiserum preabsorbed with synthetic oxytocin (100 μg/ml, obtained from Sigma).

Complete series of Vibratome sections of the experimental groups were used for quantification. Immunostained cell bodies were counted in the different hypothalamic regions; Mann-Whitney's U-test was used to determine the statistical significance.

Results

Neurons immunostained with anti-oxytocin serum could be visualized in the pvn and son in all experimental groups. All stained neurons were magnocellular, with a mean perikaryal diameter of 15 to 20 μm; parvocellular oxytocin neurons were not found. Parvocellular neurons in the suprachiasmatic nucleus showed no immunostaining with the present antibody. In sections used for immunocytochemical controls, anti-oxytocin preabsorbed with oxytocin produced no immunostaining. Due to the thickness of Vibratome sections it was often possible to trace the site of projection of immunostained neurons.

Ovariectomized control animals

Oxytocin-immunoreactive perikarya were found in the son, including the retrochiasmatic portion and in the pvn. Some oxytocin neurons appeared in the intersupraoptico-paraventricular islands (ispi). Bundles of oxytocinergic nerve fibers were seen in the ventral and lateral portion of the hypothalamus, and in the median eminence. Some oxytocin cells in the periventricular nucleus (pev, Fig. 2) extended processes toward the wall of the third ventricle. Scattered immunostained perikarya appeared in the medial preoptic area (mpoa), the lateral subcommissural nucleus (lsn), the perifornical region (pf) and in the ventromedial hypothalamus (Fig. 1). Immunostained processes of these cells were visible in the lsn, in the lateral hypothalamus and in the anteroventral zona incerta (zi).

Pregnant animals

Brain sections from rats sacrifized on day 15 of pregnancy showed a similar staining pattern as brain sections from ovariectomized controls. The number of oxytocin-immunostained cell bodies outside the pvn and son was increased at day 18 of pregnancy. Additional oxytocin-immunoreactive perikarya appeared in the preoptic region and in the ventral and medial hypothalamus. These cell bodies were adjacent to blood vessels in most cases.

Parturient animals

At parturition additional clusters of oxytocin-immunoreactive neurons attached to blood vessels occurred in the medial preoptic area, the ventral hypothalamus (Fig. 3) and the lateral subcommissural nucleus. Bundles of immunostained fibers ran parallel to or around blood vessels (Fig. 4). Oxytocinergic neurons were associated with arteries, veins and capillaries. While more cell bodies and processes were visible in parturient animals, the intensity of immunostaining was generally weaker than in pregnant or control rats. Processes appeared to be thinner and to have fewer varicosities. Only in the periventricular nucleus, immunostaining of perikarya and processes was markedly more intense at the time of parturition (Fig. 2b). Numerous processes appeared to terminate within the third ventricle or in the subependymal space. The topography of oxytocin-immunostained perikarya in the paraventricular and supraoptic nuclei and in the ispi did not differ in parturient compared to pregnant or postpartum animals.

Postpartum lactating animals

Perivascular oxytocin neurons, visible in the preoptic and anterior hypothalamic region peripartum, started to loose oxytocin immunostaining by day 2 postpartum. The perivascular oxytocin neurons remaining were located mostly in the ispi. In lactating animals numerous oxytocinergic neurons appeared without association with blood vessels in the mpoa, the lsn, the pf and throughout the lateral hypothalamus, exceeding by far the number of single neurons visible in control animals in these regions (Figs. 5, 6). In the ventral portion of the lsn multipolar oxytocinergic neurons extended projections with numerous varicosities to the medial preoptic area, while cells in the dorsal portion of this nucleus seemed to project to the lateral septum. Additional neurons with oxytocin immunostaining were found in the pf, ventral to the ansa lenticularis (al) and in the zi (Fig. 9) with processes extending to the capsula interna, into the ansa lenticularis and to the bed nucleus of the stria terminalis. Periventricular neurons and processes continued to contain intense oxytocin immunoreactivity. The distribution of oxytocin-immunostained perikarya and fibers was similar in day-5 lactating rats.

Postweaning animals

At day 30 postpartum, which was 6 days after removal of the litter from lactating mothers, the distribution and intensity of oxytocin immunostaining was indistinguishable from that seen in ovariectomized control animals.

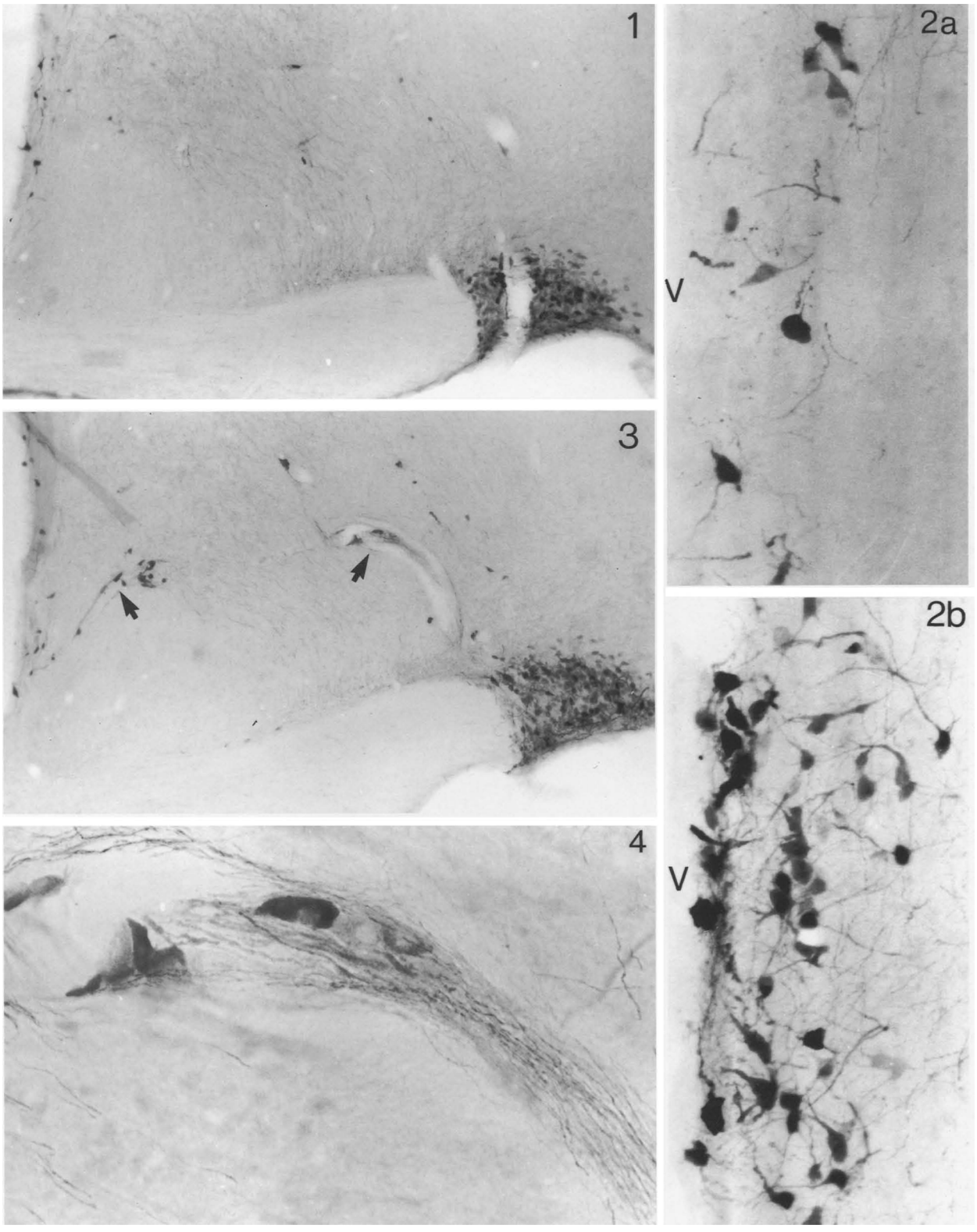

Fig. 1. Frontal section through the anterior hypothalamus of an ovariectomized rat. Oxytocin-immunoreactive neurons are visible in the supraoptic and in the periventricular nuclei. × 120

Fig. 2a, b. The periventricular hypothalamic nucleus of an animal at day 18 of pregnancy (**a**) contains only few oxytocin-immunoreactive processes and perikarya. An increased number of immunostained neurons appears in this region peripartum (**b**). Processes of these cells extend toward the third ventricle (*V*). × 320

Fig. 3. Frontal section through the anterior hypothalamus of a parturient rat. Additional oxytocinergic neurons occur as perivascular clusters in the ventromedial hypothalamus (*arrows*). × 100

Fig. 4. Group of perivascular neurons in the anterior hypothalamus of a parturient rat (detail of Fig. 3). Numerous immunostained processes without prominent varicosities extend along the blood vessel. × 900

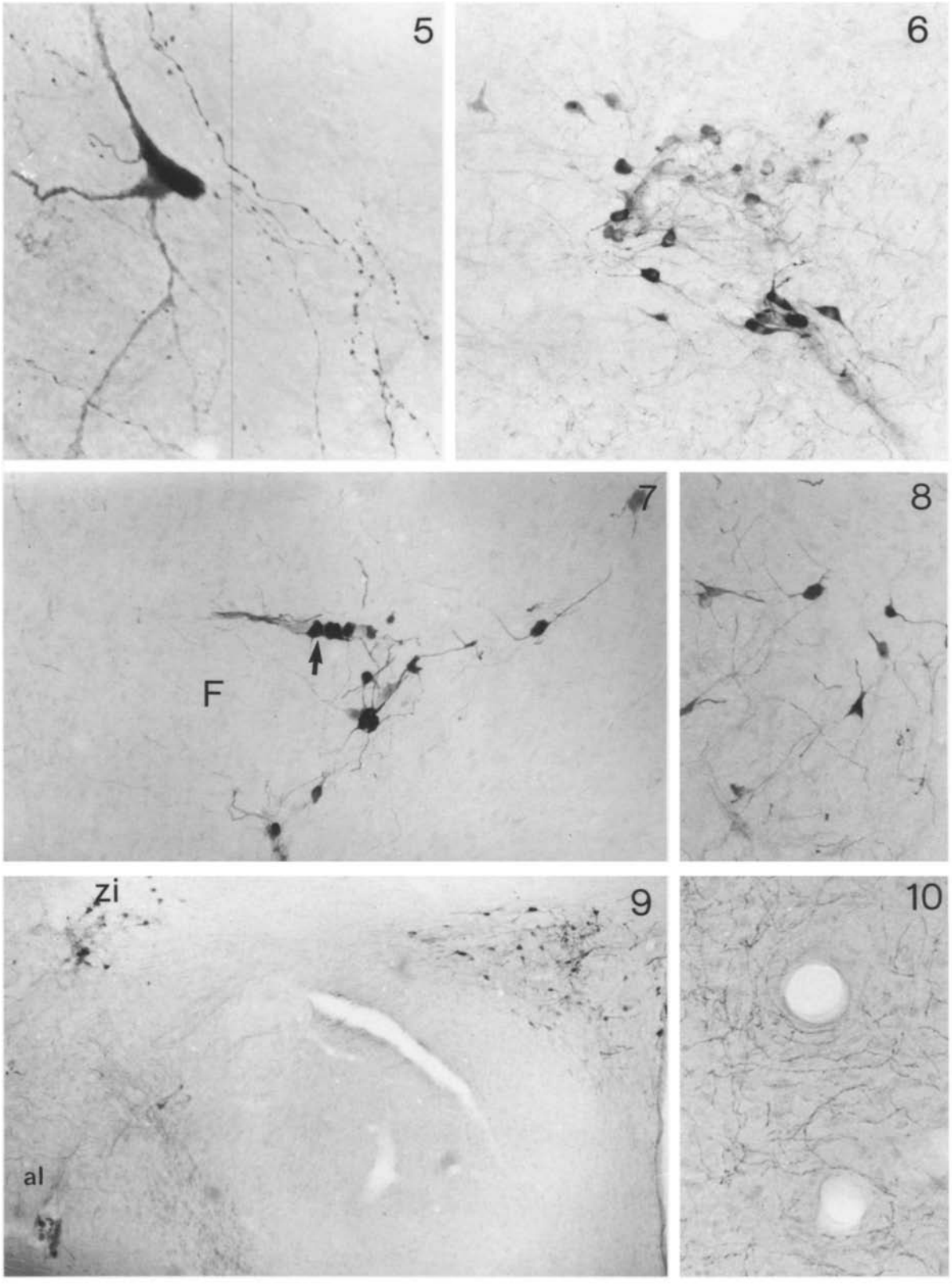

Fig. 5. Intensely immunoreactive oxytocin neuron with beaded processes in the dorsal preoptic region at day 2 of lactation. These cells have no visible connections to blood vessels. × 550

Fig. 6. Day 2 of lactation: group of oxytocin neurons in the ventrolateral hypothalamus. × 280

Fig. 7. Perifornical region of a parturient rat. Oxytocin neurons appear lateral to the fornix (*F*) as perivascular group (*arrow*) and as single neurons without visible connection to blood vessels. × 280

Fig. 8. Preoptic region of a 9-day lactating rat. While most of the blood vessels are no longer surrounded by perivascular immunoreactive neurons, numerous oxytocin cells with stained processes and predominant central projections occur in this region. × 280

Fig. 9. At day 2 of lactation, groups of oxytocin neurons not associated with blood vessels appear ventral to the ansa lenticularis (*al*) and in the ventral zona incerta (*zi*). × 120

Fig. 10. From day-2 post partum onward, most of the preoptic and anterior hypothalamic blood vessels are free of oxytocinergic neurons. Numerous immunoreactive processes appear in the neuropil. × 350

Numbers of oxytocinergic neurons in pregnant, parturient and lactating rats

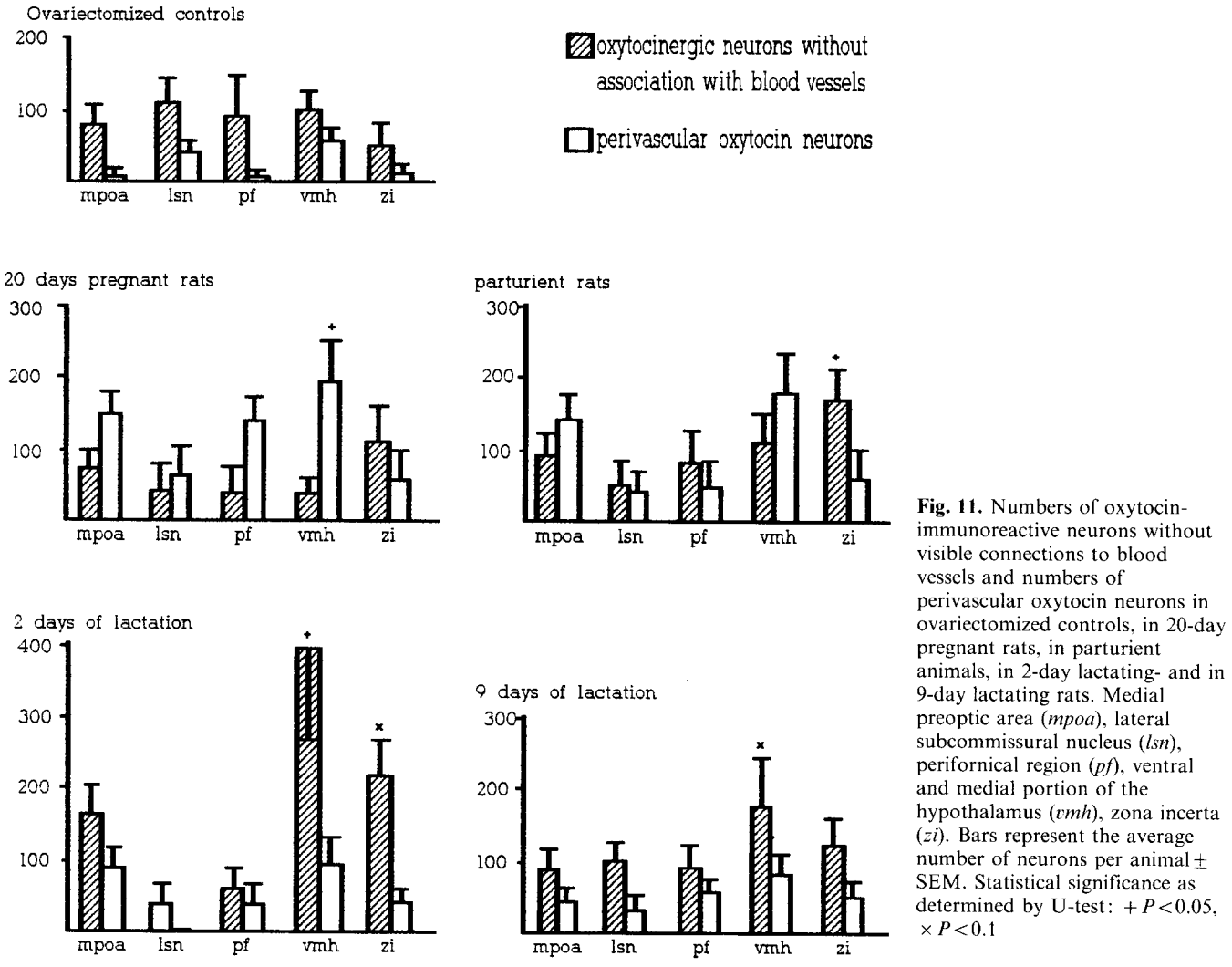

Fig. 11. Numbers of oxytocin-immunoreactive neurons without visible connections to blood vessels and numbers of perivascular oxytocin neurons in ovariectomized controls, in 20-day pregnant rats, in parturient animals, in 2-day lactating- and in 9-day lactating rats. Medial preoptic area (*mpoa*), lateral subcommissural nucleus (*lsn*), perifornical region (*pf*), ventral and medial portion of the hypothalamus (*vmh*), zona incerta (*zi*). Bars represent the average number of neurons per animal ± SEM. Statistical significance as determined by U-test: $+P<0.05$, $\times P<0.1$

Discussion

The distribution of oxytocin-immunoreactive neurons and nerve fibers observed in ovariectomized controls, day-15 pregnant, and day-30 postpartum rats is very similar to the topography of oxytocin immunostaining described previously by other investigators in normal rats (Rhodes et al. 1981; Sofroniew and Schrell 1981). While the distribution of oxytocin-immunostained neurons in the classical magnocellular nuclei son and pvn was similar in all experimental groups, impressive changes in oxytocinergic topography were observed outside of these nuclei.

Two distinct shifts in the distribution of oxytocin immunostaining occurred in the preoptic area, lateral subcommissural nucleus, and ventral and medial hypothalamus during late pregnancy, parturition and early lactation. In addition, intense oxytocin immunostaining appeared at the time of parturition in neuronal perikarya and processes in the periventricular nucleus and persisted postpartum. Each population of oxytocin neurons that undergoes a distinct pattern of change in immunostaining may be influenced differently by hormonal and other physiological alterations occurring during late pregnancy, parturition and lactation.

The first shift in the pattern of immunostaining of oxytocin was the appearance of clusters of perikarya in close association with blood vessels in the medial preoptic area, the lsn, the pf and the ventral and medial portion of the hypothalamus. Numbers of perivascular oxytocin-immunoreactive neurons (Fig. 11) in the preoptic region and anterior hypothalamus increased on day 18 of pregnancy and reached a maximum at the time of parturition. These clusters of perivascular neurons were distinct from the intersupraoptico-paraventricular islands (ispi), which form large cell aggregates around the major blood vessels in the retrochiasmatic and lateral hypothalamus (review: Dawood 1984). The widespread appearance of oxytocin-immunostained neurons in association with blood vessels may be facilitated by changes in ovarian steroid levels during late pregnancy and parturition (Bridges 1984). The mechanism underlying the increase in number of oxytocin-immuno-

stained perivascular neurons is not clear. Perhaps a population of perivascular neurons with the potential for synthesizing oxytocin is selectively stimulated by the hormonal conditions. However, it is possible that several factors increase the number of immunocytochemically detectable perivascular oxytocin neurons in the anterior hypothalamus. Kamei (1986) described such an increase in male rats after water deprivation.

Although the largest number of perivascular oxytocin-immunostained neurons was visible around the time of parturition, the intensity of immunostaining was diminished compared to day 18 of pregnancy. The weaker immunostaining and the decreased visibility of varicosities may reflect high secretory activity in all oxytocinergic neurons near parturition. This question can be solved by assessing the amount of m-RNA by means of in situ hybridization. The question whether oxytocin, released from perivascular neurons, gains access to the systemic or portal circulation cannot be answered in the present study.

Kamei (1986) suggested that oxytocin, secreted intravascularly from perivascular neurons in thirsting rats, stimulates neurons in hypothalamic nuclei supplied by the respective blood vessels. Furthermore, a possible vasoactive action of perivascular oxytocin influencing central blood pressure regulation should also be taken into consideration.

The second shift in the distribution of oxytocin-immunoreactive neurons in the medial preoptic area, the lateral subcommissural nucleus and the ventral and medial hypothalamus occurred between parturition and the second day postpartum. Discrete, often multipolar perikarya appeared scattered throughout the neuropil. Most of the perivascular magnocellular neurons did not react with anti-oxytocin serum, indicating that cytoplasmic levels of oxytocin in these cells fall below immunocytochemical detectability. It is likely that these cells stop synthesizing oxytocin after the decline in both estrogen and progesterone after parturition (Gerber 1979). The strongly immunoreactive neurons appearing postpartum are certainly distinct from the immunostained neurons visible around parturition since the former do not seem to be associated with blood vessels but have, as far as we can determine from Vibratome sections, projections within the CNS. The number of these neurons was significantly higher than in ovariectomized controls suggesting an activation of oxytocinergic systems with central projections post partum.

We have previously observed a significant rise in immunoreactive oxytocin content in the lateral septum after parturition (Caldwell et al. 1987). Perhaps transport of oxytocin along axons from the lateral subcommissural nucleus contributes to the postpartum rise in oxytocin content in the ventral lateral septum. The increased number of oxytocin neurons with probable central projections, observed in the preoptic region after parturition, may be involved in the regulation of a number of behavioral and physiological changes that unfold post partum. The onset of maternal behavior, for instance, depends upon oxytocin release within the limbic system (Pedersen et al. 1985; Fahrbach et al. 1985; Van Leengood et al. 1987). Lesions of the lateral subcommissural nucleus or the septum disrupt maternal behavior (Terkel et al. 1979). Centrally projecting oxytocin neurons may also be involved in the conditioned milk ejection reflex that develops after a brief period of post partum nursing experience (Slotnick 1975).

Intense immunostaining for oxytocin appears in the periventricular nucleus at the time of parturition. Numerous oxytocin-immunoreactive processes seem to project toward the third ventricle. The question whether oxytocinergic processes enter the ventricle, similar to CSF-contacting neurons (Vigh-Teichmann and Vigh 1974), or end in the subependymal space has to be addressed by electron microscopy. A rise in oxytocin concentration in the CSF has been reported to occur at parturition (Unger et al. 1976).

Estrogen treatment for two days increased the number of centrally projecting oxytocin neurons in the lateral subcommissural nucleus, medial preoptic area and ventromedial hypothalamus as well as in the periventricular nucleus (Jirikowski et al. 1988). The location of oxytocin-immunoreactive neurons within these brain areas was very similar in estrogen-treated and postpartum rats. It is, therefore, likely that the postpartum increase in immunoreactivity of oxytocin neurons outside of the classical magnocellular nuclei is facilitated by the high levels of estrogen occurring near parturition. However, immunoreactivity of this population of oxytocin neurons persisted through day 5 postpartum, which is several days after plasma estrogen falls to very low levels (Gerber 1979). Additional investigation will be necessary to determine if increased immunoreactivity of these neurons persists throughout lactation or if it declines at some time prior to weaning. It will be of interest to determine whether nipple stimulation or other stimuli from offspring are necessary for the persistence of increased oxytocin immunoreactivity postpartum.

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