Evidence for the involvement of histaminergic neurones in the regulation of the rat oxytocinergic system during pregnancy and parturition

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1. Previous studies have shown that histaminergic neurones of the tuberomammillary nucleus project directly to hypothalamic magnocellular nuclei and that intracerebroventricular administration of histamine increases the synthetic activity of magnocellular oxytocin neurones.

2. Histaminergic neurones of the dorsomedial tuberomammillary nucleus that project to the magnocellular region of the paraventricular nucleus are activated during late pregnancy and lactation, as measured by an increase in mRNA for the synthetic enzyme histidine decarboxylase.

3. There is a concomitant increase in oxytocin mRNA in magnocellular neurones of the paraventricular nucleus. This increase in mRNA contributes to an accumulation of oxytocin before birth and to continued oxytocin synthesis during lactation.

4. Intracerebroventricular administration of mepyramine, a specific antagonist of the H_1 histamine receptor, causes a delay in the birth of subsequent pups if given to the mother during parturition. Vehicle or the H_2 receptor antagonist cimetidine has no effect. Thus, histamine acts centrally, via H_1 receptors, during parturition and may have an excitatory effect on oxytocin release.

5. These results suggest that afferent histaminergic neurones show increased activity during pregnancy and may be responsible for the increase of synthesis in magnocellular oxytocin neurones at this time. If, as previously reported, these histamine neurones can reduce the electrical activity of oxytocin neurones via H_2 receptors, then they may have a dual effect, increasing the synthesis of oxytocin while inhibiting its premature release. At term, any inhibitory effects of histamine are overcome to allow oxytocin secretion.

In order to avoid the premature release of oxytocin close to term and before the birth canal is prepared for the passage of the pups, the rat has complex opioid peptide-mediated mechanisms to inhibit the activity of magnocellular oxytocin neurones (Bicknell, Leng, Russell, Dyer, Mansfield & Zhao, 1988; Bicknell, Onaka, Leng, Luckman & Douglas, 1993; Douglas, Dye, Leng, Russell & Bicknell, 1993). During pregnancy the inhibition is exerted primarily at the level of the pituitary, but as term approaches this is reduced and endogenous opioids act at the hypothalamic level to prevent magnocellular oxytocin neurone activity (Luckman *et al.* 1993). This allows the build up of pituitary oxytocin and prevents its release until the opioid inhibition is removed. However, the increase in magnocellular neurone oxytocin content may not be due entirely to an inhibition of release, since there is evidence that the magnocellular neurones also increase synthesis during pregnancy, reflected by increased expression of oxytocin mRNA (Van Tol, Bolwerk, Liu & Burbach, 1988; Zingg & Lefebvre, 1988) and transcript polyadenylation (Zingg & Lefebvre, 1989). Furthermore, it is hypothesized that the oxytocinergic system may require morphological adaptations in preparation for parturition that will require altered synthetic activity (Theodosis & Poulain, 1984; Theodosis, Chapman, Montagnese, Poulain & Morris, 1986). It might be assumed that changes in the synthetic activity of these neurones in pregnancy must be brought about by the changing sex steroid milieu, but since magnocellular oxytocin neurones lack nuclear gonadal steroid receptors themselves (Rhodes, Morrell & Pfaff, 1981; Sar, 1988; Fox, Harlan, Shivers & Pfaff, 1990; Bethea, Kohama & Widmann, 1994) this is likely to be an indirect effect via synaptic inputs.

Intracerebroventricular (I.C.V.) administration of histamine can increase the synthetic activity of magnocellular oxytocin neurones of the paraventricular nucleus (PVN) and supraoptic nucleus (SON), as measured by increases in the

expression of the protein product of the c-*fos* gene (Kjaer, Larsen, Knigge, Moller & Warberg, 1994*a*) and oxytocin mRNA (Kjaer, Larsen, Knigge & Warberg, 1994*b*). The effect on oxytocin mRNA appears to be mediated by both H_1 and H_2 histamine receptors (A. Kjaer, unpublished observations). Histaminergic neurones are located exclusively in the tuberomammillary region caudal to the hypothalamus and project to almost all areas of the central nervous system (Watanabe *et al.* 1984; Schwartz, Arrang, Garbarg, Pollard & Ruat, 1991; Wada, Inagaki, Yamatodani & Watanabe, 1991). Histaminergic neurones of the tuberomammillary nucleus (TMN) have been shown to project directly to the PVN and SON; there is a particularly strong connection between the dorsomedial TMN and the magnocellular portion of the PVN, while ventrolateral TMN neurones project to the SON (Ericson, Watanabe & Kohler, 1987; Weiss, Yang & Hatton, 1989).

We have looked indirectly at the activity of histamine neurones in the dorsomedial TMN by measuring the mRNA for the synthetic enzyme histidine decarboxylase using *in situ* hybridization in virgin, pregnant and lactating rats. We have compared histamine decarboxylase mRNA in the dorsomedial TMN with oxytocin mRNA in the magnocellular portion of the PVN, because these regions have the strongest anatomical links (Ericson *et al.* 1987). To assess any acute actions of central histamine on the progress of parturition, specific histamine receptor antagonists were administered to the mother during birth. These results have been presented elsewhere in abstract form (Luckman & Larsen, 1995).

METHODS

Experimental animals

Female Wistar rats were mated over a single night period so that, under a 14 h light:10 h dark regime, parturition would occur 21 days later. Pregnant females were individually caged and allowed free access to food and water. Experimental procedures were carried out in accordance with the Animals (Scientific Procedures) Act (1986).

Histidine decarboxylase and oxytocin mRNA *in situ* hybridization

Virgin female rats ($n = 8$), day 7 pregnant ($n = 5$), day 21 pre-parturient pregnant ($n = 8$) and day 5 lactating females ($n = 6$) were killed by cervical dislocation and decapitation. Their brains were removed rapidly from the skull, frozen with dry ice and stored at −80 °C.

Coronal sections 12 μm thick were cut on a cryostat to include the magnocellular regions of the PVN (equivalent to Plates 25 and 26 of the atlas of Paxinos & Watson, 1986) and the dorsomedial region of the TMN (equivalent to the tuberal magnocellular nucleus of Paxinos & Watson, 1986; Plate 33). The sections were thaw-mounted onto gelatin-coated slides, fixed in 4% (w/v) paraformaldehyde in sodium phosphate-buffered saline (PBS; 140 mM NaCl, 2·7 mM KCl, 10 mM Na_2HPO_4 and 1·8 mM KH_2PO_4; pH 7·4) and rinsed twice in PBS. Hybridizations were initiated by placing the sections in 0·25% (v/v) acetic anhydride in 0·1 M triethanolamine–0·9% NaCl, pH 8·0 for 10 min at room temperature, followed by delipidation through a series of graded ethanols (70, 80, 95 and 100%) and chloroform. Synthetic DNA oligonucleotide probes directed against rat oxytocin bases 247–294 (Ivell & Richter, 1984) or histidine decarboxylase bases 50–97 (Joseph *et al.* 1990) were used in the hybridization experiments. The probes were labelled with ^{35}S-αthio-ATP (> 3000 Ci mmol^{-1}; NEN Du Pont) using terminal deoxynucleotidyl transferase (Boehringer Mannheim) to a specific activity of approximately $2{\cdot}0 \times 10^{19}$ d.p.m. mol^{-1}. Sections were hybridized with $0{\cdot}5$–$1{\cdot}0 \times 10^7$ d.p.m. ml^{-1} at 37 °C in a buffer (pH 7·2) containing 25% (v/v) formamide, 4 × standard saline–sodium citrate buffer (SSC; 1 × SSC = 0·15 M NaCl, 0·015 M sodium citrate, pH 7·2), 1 × Denhardt's solution (Sigma), 10% (w/v) dextran sulphate, 10 mM dithiothreitol, 500 μg ml^{-1} salmon sperm DNA and 250 μg ml^{-1} yeast tRNA. After hybridization, slides were washed four times in 1 × SSC at 55 °C for 15 min and twice at room temperature for 30 min. The sections were dipped briefly into water, dried and exposed to Hyperfilm® (Amersham) for 4 days (oxytocin) or 3 weeks (histidine decarboxylase). Sections from all animals were hybridized concomitantly and exposed to the same film. After exposure to film, the sections were dipped in Amersham LM2 fluid emulsion and exposed for twice as long as the films, before being developed in D19 (Kodak). Film autoradiograms of oxytocin mRNA expression in the PVN were quantified using a computer-assisted image analysis system (Image 1.59; Wayne Rasband, National Institutes of Health, MD, USA) and grain densities converted to d.p.m. (mg wet weight)$^{-1}$ using ^{35}S-brain paste standards as reference. The densities of emulsion siver grains over neurones positively hybridized for histidine decarboxylase mRNA were assessed by using a camera-equipped microscope with Image 1.59 software. Background values from neighbouring areas free from positive hybridization were subtracted from individual sections, thus serving as their own internal standards. Direct comparisons of histidine decarboxylase and oxytocin mRNA expression in individual groups were facilitated by arbitrarily setting hybridization levels in control virgin animals as 100%.

Histamine receptor antagonist administration during parturition

Two days before the expected day of parturition, pregnant rats ($n = 20$) had guide tubes (external cannula, 26 gauge; Semat Technical Ltd, St Albans, UK) placed at the junction between the third and lateral ventricles (co-ordinates according to Paxinos & Watson, 1986; 0·6 mm posterior and 1·6 mm lateral to bregma, 4·6 mm below surface of skull) under halothane (1%) anaesthesia. The cannulae were fixed in position with two screws and dental cement and blocked with an obturator. During the expected day of parturition, the conscious, freely moving rats were watched under white artificial lighting during the day and under reduced red lighting during the normal night period. On the birth of the first pup, the obturator was removed and an internal cannula (33 gauge; Semat Technical) was inserted into the guide tube. The internal cannula was attached to a 10 μl syringe via sufficient polyethylene tubing to avoid restricting the movements of the mother. On birth of the second pup 2·5 μl of histamine receptor antagonist or saline vehicle (0·9% NaCl) was administered I.C.V. over an approximate 30 s period. The H_1 receptor antagonist, mepyramine (350 nmol in 2·5 μl; DAK Laboratories, Copenhagen, Denmark), and the H_2 antagonist, cimetidine (400 nmol in 2·5 μl; SmithKline Beecham), were used at concentrations previously determined to block histamine-induced oxytocin secretion (Kjaer, Knigge & Warberg, 1995). The behaviour of the mother and the time of birth of subsequent pups were recorded.

RESULTS

In situ hybridization

Silver grains denoting the presence of oxytocin mRNA were clearly present over both the magnocellular and parvocellular portions of the PVN (Fig. 1). Analysis of optical densities from the autoradiogram detected an increase in the expression of oxytocin mRNA in the magnocellular region of the PVN during pregnancy and into lactation (Fig. 2). Analysis of variance revealed that there were significantly more silver grains present in the day 21 pregnant and day 5 lactating groups compared with the control virgin group (ANOVA with *post hoc* Dunnett's multiple comparisons test, both $P < 0{\cdot}01$).

Analysis of emulsion-dipped slides showed a distinctive cluster of neurones containing histidine decarboxylase mRNA in the dorsomedial TMN on either side of the caudal third ventricle (Fig. 3). While there were no increases in silver grains denoting the presence of histidine decarboxylase mRNA in the early stages of pregnancy, at the end of pregnancy and in lactation there was a greater than twofold increase (both $P < 0{\cdot}01$; Fig. 2).

Histamine receptor antagonist injections

The I.C.V. injection of mepyramine, but not cimetidine, caused a significant increase in the time interval to the birth of the subsequent pup (Fig. 4). The intervals between the births of pups 2 and 3 were 8 ± 1, 27 ± 7** and 6 ± 1 min for the vehicle, mepyramine and cimetidine groups, respectively (** $P < 0{\cdot}01$ compared with vehicle-treated group using ANOVA with *post hoc* Dunnett's multiple comparisons test). The intervals between the births of pups 2 and 4 were 16 ± 2, 37 ± 8* and 18 ± 2 min (* $P < 0{\cdot}05$). After the initial delay, birth progressed as normal with the

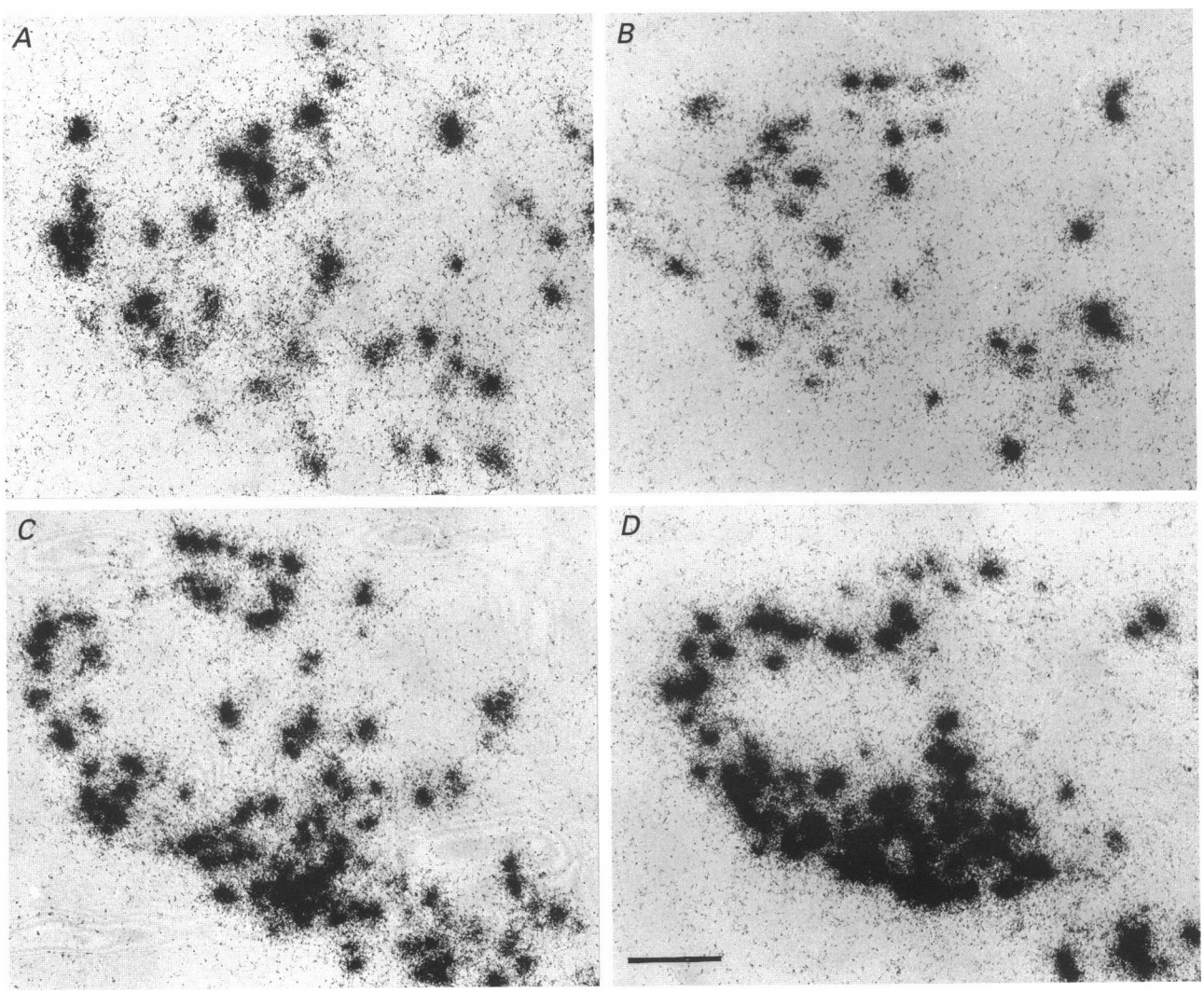

Figure 1. Expression of oxytocin mRNA in the hypothalamic PVN

Representative sections are from virgin (*A*), day 7 pregnant (*B*), day 21 pregnant (*C*) and day 5 lactating (*D*) female rats. Each panel shows one PVN on coronal sections taken from the same rostrocaudal level. Scale bar represents 100 μm.

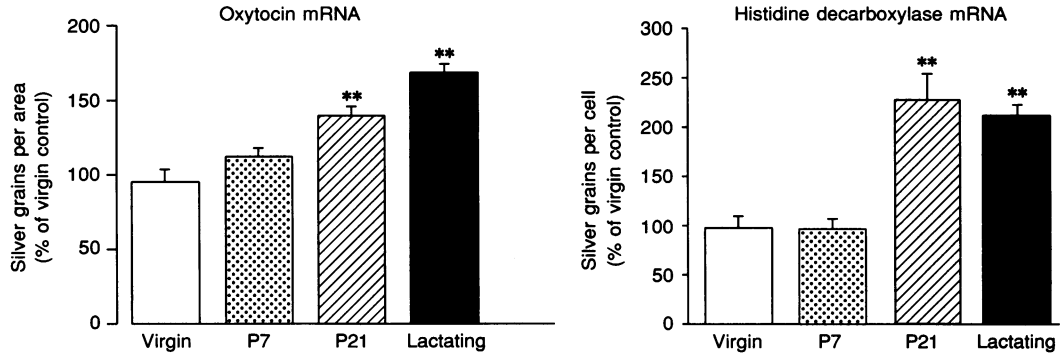

Figure 2. Results from an *in situ* hybridization experiment

Histograms show oxytocin and histidine decarboxylase mRNA quantification in the magnocellular PVN and dorsomedial TMN, respectively, from virgin, day 7 pregnant (P7), day 21 pregnant (P21) and day 5 lactating female rats. Values have been normalized to control levels to allow comparison (the mean for the virgin group equals 100%). Bars represent means + S.E.M. ** $P < 0{\cdot}01$ compared with expression in the virgin female group using ANOVA with *post hoc* Dunnett's multiple comparisons test.

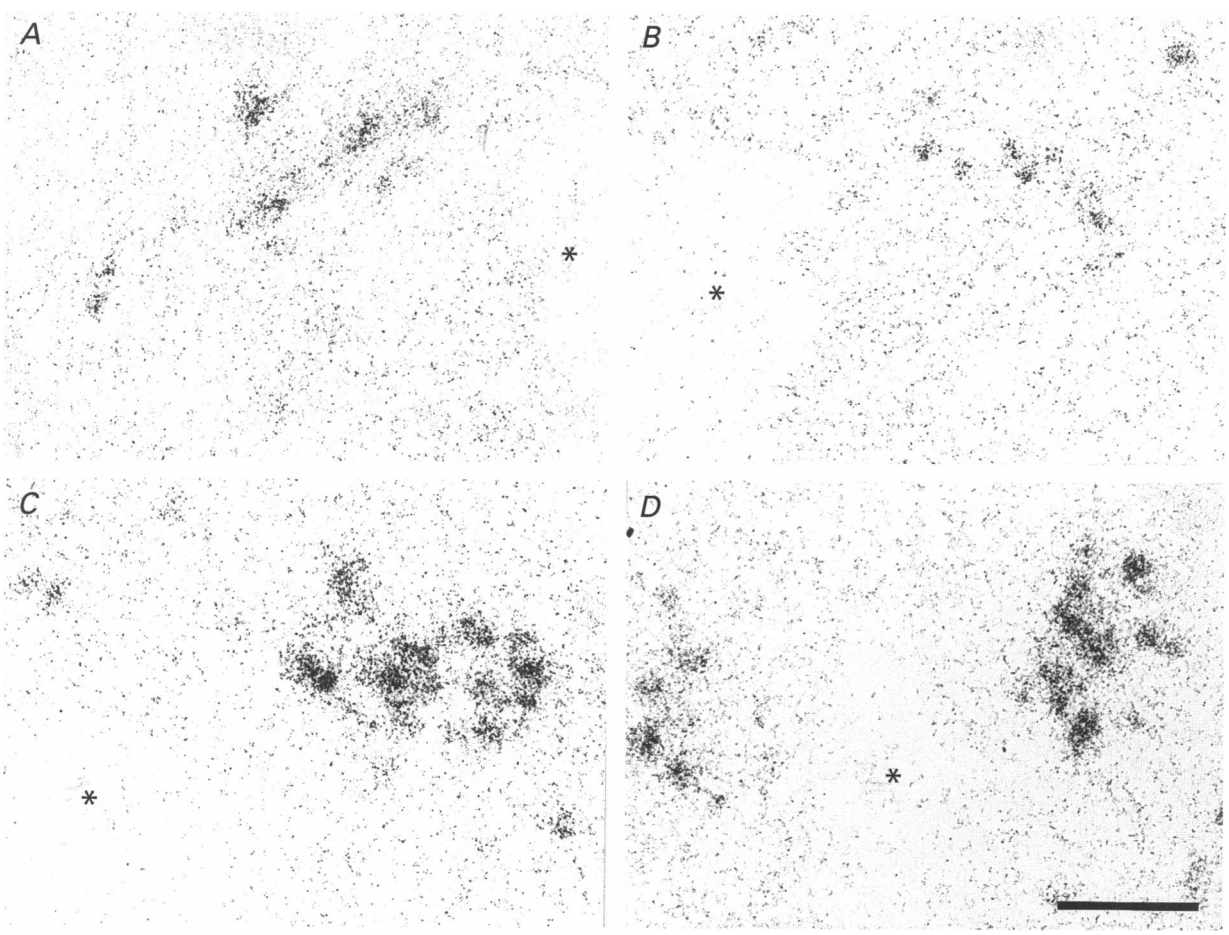

Figure 3. Expression of histidine decarboxylase mRNA in the dorsomedial TMN of the caudal hypothalamus

Representative sections from virgin (*A*), day 7 pregnant (*B*), day 21 pregnant (*C*) and day 5 lactating (*D*) female rats. Each coronal section is taken from a comparable rostrocaudal level. Asterisks depict the third ventricle. Scale bar represents 100 μm.

parturient mothers showing no obvious differences in behaviour between the groups. Mean litter size was the same in each group 90 min following the birth of the second pup (9 ± 1, 9 ± 1 and 10 ± 1, respectively).

DISCUSSION

Histaminergic neurones of the TMN project directly to the hypothalamic PVN and SON (Ericson *et al.* 1987; Weiss *et al.* 1989), the nuclei that contain the major populations of magnocellular oxytocin neurones. These oxytocin neurones play an integral part in the control of parturition and lactation, since the release of their neurohormone product causes uterine and mammary smooth muscle contraction. We show that during pregnancy and lactation there is an increase in the expression of histidine decarboxylase mRNA, the synthetic enzyme of histamine, in dorsomedial TMN neurones. This parallels an increase in the expression of oxytocin mRNA seen in magnocellular neurones to which the histaminergic neurones project. Previously, the I.C.V. administration of histamine has been shown to increase the abundance of c-fos protein and oxytocin mRNA in magnocellular neurones (Kjaer *et al.* 1994*a*, *b*). Thus, assuming the increase in histidine decarboxylase is indicative of a change in the output of histamine neurones, it is possible that this histaminergic projection may be responsible for the rise in oxytocin mRNA content (this study; Van Tol *et al.* 1988; Zingg & Lefebvre, 1988, 1989).

In addition to increases in the expression of oxytocin itself, the oxytocin neurone is likely to require other changes in its synthetic activity during pregnancy. For example, there are well-documented changes in the morphology of oxytocin neurones that may be responsible for the unique ability of these neurones to adapt their action potential patterning to include synchronized bursting (Theodosis & Poulain, 1984). The morphological changes include closer apposition of oxytocinergic cell bodies and a greater sharing of available synaptic input. In this context, it is interesting to note that synaptically released histamine is able to increase dye coupling amongst vasopressin neurones of the SON via H_1 receptors (Hatton & Yang, 1996), though the morphological changes that occur during pregnancy in the SON and PVN are widely believed to involve only oxytocin neurones (Theodosis *et al.* 1986).

The activation of an input to oxytocin neurones before parturition is timed to occur has very important physiological implications, since premature release of oxytocin has to be avoided. This problem could possibly be overcome if, while causing an increase in synthetic activity, the same input electrically inhibits the neurones. Thus, it is interesting that histamine from TMN neurones can have an inhibitory effect on the electrical activity of oxytocin neurones (Yang & Hatton, 1994), although the available data are from supraoptic and not paraventricular neurones. Electrical stimulation of the TMN in the horizontal slice preparation produces constant latency, fast inhibitory postsynaptic potentials (IPSPs) in antidromically and immunohistochemically identified oxytocin neurones. These IPSPs can be blocked by H_2 histamine receptor antagonism and by chloride channel blockers and are reversed by low chloride perifusion, suggesting that there is a direct hyperpolarizing action of histamine on oxytocin neurones (Yang & Hatton, 1994). In this way, a single input may be able to increase the synthetic activity of the oxytocin neurones while preventing premature neurohormone release. Such a dual effect might possibly be due to differential coupling of receptor subtypes (Schwartz *et al.* 1991). Although the mode of administration of drugs should be taken into account (I.C.V. injections may not only be affecting oxytocin neurones directly), both H_1 and H_2 histamine receptors are able to increase the synthetic activity of oxytocin neurones (A. Kjaer, unpublished observations), while H_2 histamine receptors mediate the inhibitory effect on electrical activity (Yang & Hatton, 1994). Thus, histamine may act in concert with endogenous opioid systems also known to inhibit premature oxytocin release (Bicknell *et al.* 1988, 1993; Douglas *et al.* 1993).

If histamine is able to have this dual effect during pregnancy, then at term the inhibitory effect of H_2 histamine receptors on oxytocin neurones must be overcome. This could be achieved by the uncoupling of the receptors, a change in their abundance or by the dominance of a more

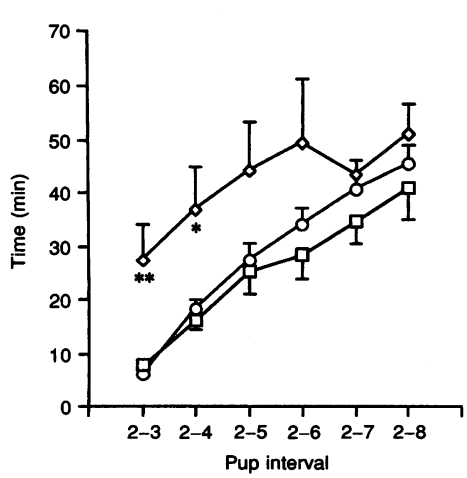

Figure 4. Rat pup birth data

Vertical axis denotes time of birth of the pup marked on the horizontal axis from the time of the second pup. □, vehicle-treated group; ◇, mepyramine-treated group; ○, cimetidine-treated group. Points represent means ± S.E.M. * $P < 0{\cdot}05$ and ** $P < 0{\cdot}01$ compared with vehicle-treated group using ANOVA with *post hoc* Dunnett's multiple comparisons test.

powerful excitatory input. Our results using the injection of specific histamine receptor antagonists suggest that endogenous histamine may have a positive effect on the progress of parturition via the H_1 receptor. The delay in the birth of subsequent pups following a single injection of antagonist was small compared with that of other agents, such as morphine (Luckman *et al.* 1993), and parturition then continued as normal. The I.C.V. injection of the antagonist does not determine the point at which endogenous histamine may be acting. However, we cannot discount a direct, excitatory effect of histamine via H_1 receptors on the electrical activity of oxytocin neurones at term, in a manner similar to that seen on vasopressin neurones at other times (Armstrong & Sladek, 1985; Smith & Armstrong, 1993; Li & Hatton, 1996). Further electrophysiological experiments will need to be carried out on female rat tissue and at different times during pregnancy. Although the induction of c-*fos* need not correlate directly with electrical activity, a H_1 receptor agonist can induce c-*fos* mRNA in the oxytocinergic neurones of virgin female rats (S. Luckman, unpublished observations). Recently, Schagen, Knigge, Kjaer, Larsen & Warberg (1996) have found a reduction in suckling-induced oxytocin release following I.C.V. administration of both mepyramine and cimetidine, suggesting a continuing role of histamine in oxytocin neuronal function into lactation. This is supported by our finding here that histidine decarboxylase mRNA remains high during lactation.

The physiological importance of histamine actions on the functioning of oxytocin neurones has to be determined further. In particular, it will be necessary to investigate whether the actions of histamine on the synthetic activity of oxytocin neurones is a direct one, in part by determining which receptors these neurones express. If, as suggested by the literature, histamine can increase the synthetic activity of the neurone while inhibiting its electrical activity then this will prove to be an important example of the dual control of target neurones by a single transmitter.

ARMSTRONG, W. E. & SLADEK, C. D. (1985). Evidence for excitatory actions of histamine on supraoptic neurons *in vitro*: mediation by an H_1-type receptor. *Neuroscience* **16**, 307–322.

BETHEA, C. L., KOHAMA, S. G. & WIDMANN, A. A. (1994). Search for progestin receptors (PR) in prolactin-releasing peptidergic neurons: oxytocin neurons lack PR, but respond to gonadal steroids in monkeys. *Endocrinology* **134**, 945–953.

BICKNELL, R. J., LENG, G., RUSSELL, J. A., DYER, R. G., MANSFIELD, S. & ZHAO, B. (1988). Hypothalamic opioid mechanisms controlling oxytocin neurones during parturition. *Brain Research Bulletin* **20**, 743–749.

BICKNELL, R. J., ONAKA, T., LENG, G., LUCKMAN, S. M. & DOUGLAS, A. J. (1993). Pregnancy-associated opioid restraint of oxytocin neurones involves a presynaptic action on brainstem catecholaminergic afferents. *Society for Neuroscience Abstracts* **19**, 1791, 734.4.

DOUGLAS, A. J., DYE, S., LENG, G., RUSSELL, J. A. & BICKNELL, R. J. (1993). Endogenous opioid regulation of oxytocin secretion through pregnancy in the rat. *Journal of Neuroendocrinology* **5**, 307–314.

ERICSON, H., WATANABE, T. & KOHLER, C. (1987). Morphological analysis of the tuberomammillary nucleus in the rat brain: delineation of subgroups with antibody against L-histidine decarboxylase as a marker. *Journal of Comparative Neurology* **263**, 1–24.

FOX, S. R., HARLAN, R. E., SHIVERS, B. D. & PFAFF, D. W. (1990). Chemical characterization of neuroendocrine targets for progesterone in the female rat brain and pituitary. *Neuroendocrinology* **51**, 276–283.

HATTON, G. I. & YANG, Q. Z. (1996). Synaptically released histamine increases dye coupling among vasopressinergic neurons of the supraoptic nucleus: mediation by H_1 receptors and cyclic nucleotides. *Journal of Neuroscience* **16**, 123–129.

IVELL, R. & RICHTER, D. (1984). Structure and comparison of the oxytocin and vasopressin genes from the rat. *Proceedings of the National Academy of Sciences of the USA* **81**, 2006–2010.

JOSEPH, D. R., SULLIVAN, P. M., WANG, Y. M., KOZAK, C., FENSTERMACHER, D. A., BEHRENDSEN, M. E. & ZAHNOW, C. A. (1990). Characterization and expression of the complementary DNA encoding rat histidine decarboxylase. *Proceedings of the National Academy of Sciences of the USA* **87**, 733–737. (Published erratum appears in *Proceedings of the National Academy of Sciences of the USA* (1990) **87**, 7346).

KJAER, A., KNIGGE, U. & WARBERG, J. (1995). Involvement of oxytocin in histamine- and stress-induced ACTH and prolactin secretion. *Neuroendocrinology* **61**, 704–713.

KJAER, A., LARSEN, P. J., KNIGGE, U., MOLLER, M. & WARBERG, J. (1994*a*). Histamine stimulates c-*fos* expression in hypothalamic vasopressin-, oxytocin-, and corticotropin-releasing hormone-containing neurons. *Endocrinology* **134**, 482–491.

KJAER, A., LARSEN, P. J., KNIGGE, U. & WARBERG, J. (1994*b*). Histaminergic activation of the hypothalamic–adrenal axis. *Endocrinology* **135**, 1171–1177.

LI, Z. & HATTON, G. I. (1996). Histamine-induced prolonged depolarization in rat supraoptic neurons: G-protein-mediated, Ca^{2+}-independent suppression of K^+ leakage conductance. *Neuroscience* **70**, 145–158.

LUCKMAN, S. M., ANTONIJEVIC, I., LENG, G., DYE, S., DOUGLAS, A. J., RUSSELL, J. A. & BICKNELL, R. J. (1993). The maintenance of normal parturition in the rat requires neurohypophysial oxytocin. *Journal of Neuroendocrinology* **5**, 7–12.

LUCKMAN, S. M. & LARSEN, P. J. (1995). Central histaminergic effects on oxytocin neurones. *Journal of Reprodroduction and Fertility* **16**, 14.

PAXINOS, G. & WATSON, C. (1986). *The Rat Brain in Stereotaxic Coordinates*. Academic Press, New York.

RHODES, C. H., MORRELL, J. I. & PFAFF, D. W. (1981). Distribution of estrogen-concentrating, neurophysin-containing magnocellular neurons in the rat hypothalamus as demonstrated by a technique combining steroid autoradiography and immunohistology in the same tissue. *Neuroendocrinology* **33**, 18–23.

SAR, M. (1988). Distribution of progestin-concentrating cells in rat brain: colocalization of [3H]ORG.2058, a synthetic progestin, and antibodies to tyrosine hydroxylase in hypothalamus by combined autoradiography and immunocytochemistry. *Endocrinology* **123**, 1110–1118.

SCHAGEN, F. H. E., KNIGGE, U., KJAER, A., LARSEN, P. J. & WARBERG, J. (1996). Involvement of histamine in suckling-induced release of oxytocin, prolactin and adrenocorticotropin in lactating rats. *Neuroendocrinology* **63**, 550–558.

SCHWARTZ, J., ARRANG, J., GARBARG, M., POLLARD, H. & RUAT, M. (1991). Histaminergic transmission in the mammalian brain. *Physiological Reviews* **71**, 1–51.

SMITH, B. N. & ARMSTRONG, W. E. (1993). Histamine enhances the depolarizing afterpotential of immunohistochemically identified vasopressin neurons in the rat supraoptic nucleus via H_1-receptor activation. *Neuroscience* **53**, 855–864.

THEODOSIS, D. T., CHAPMAN, D. B., MONTAGNESE, C., POULAIN, D. A. & MORRIS, J. F. (1986). Structural plasticity in the hypothalamic supraoptic nucleus at lactation affects oxytocin- but not vasopressin-secreting neurons. *Neuroscience* **17**, 661–678.

THEODOSIS, D. T. & POULAIN, D. A. (1984). Evidence for structural plasticity in the supraoptic nucleus of the rat hypothalamus in relation to gestation and lactation. *Neuroscience* **11**, 183–193.

VAN TOL, H. M. H., BOLWERK, E. M., LIU, B. & BURBACH, J. P. H. (1988). Oxytocin and vasopressin gene expression in the hypothalamic–neurohypophyseal system of the rat during the estrous cycle, pregnancy, and lactation. *Endocrinology* **122**, 945–951.

WADA, H., INAGAKI, N., YAMATODANI, A. & WATANABE, T. (1991). Is the histaminergic neuron system a regulatory center for whole brain activity? *Trends in Neurosciences* **14**, 415–418.

WATANABE, T., TAGUCHI, Y., SHIOSAKA, S., TANAKA, J., KUBOTA, H., TERANO, Y., TOHYAMA, M. & WADA, H. (1984). Distribution of the histaminergic neuron system in the central nervous system of rats: a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. *Brain Research* **295**, 13–25.

WEISS, M. L., YANG, Q. Z. & HATTON, G. I. (1989). Magnocellular tuberomammillary nucleus input to the supraoptic nucleus in the rat: anatomical and *in vitro* electrophysiological investigations. *Neuroscience* **31**, 299–311.

YANG, Q. Z. & HATTON, G. I. (1994). Histamine mediates fast synaptic inhibition of rat supraoptic oxytocin neurons via chloride conductance activation. *Neuroscience* **61**, 955–964.

ZINGG, H. H. & LEFEBVRE, D. L. (1988). Oxytocin and vasopressin gene expression during gestation and lactation. *Molecular Brain Research* **4**, 1–6.

ZINGG, H. H. & LEFEBVRE, D. L. (1989). Oxytocin mRNA: increase of polyadenylate tail size during pregnancy and lactation. *Molecular and Cellular Endocrinology* **65**, 59–62.

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