ends to ciliate macronuclear DNA and their role in replication will help clarify telomere structure and function in general.

Earlier proposals for telomere structure mainly stemmed from the hairpin priming^{1,5} model for the replication of chromosome ends (see Fig.2). Although there is evidence for terminal hairpins in several viruses and some evidence also in yeast chromosomes⁶, and in the *Tetrahymena* plasmid (and also at one end of *Paramecium* mitochondrial DNA), the structure of the *Oxytricha* fragments is such that they could not fold back to form hairpins. Telomeres lacking hairpins or inverted repeats might use a nucleotide covalently attached to a DNA-binding protein, as observed in adenovirus⁷ and phage ϕ 29 (ref. 8), as a primer; the covalent attachment of a protein, by preventing the ligation of telomeres, would also explain their stability compared with broken ends just as well as do the hairpin models.

Szostak and Blackburn ingeniously tested the possibility that a simple covalently bonded terminal hairpin could serve as a telomere by constructing an artificial hairpin from part of *Escherichia coli*'s β -galactosidase gene and attaching it to one end of their linear plasmid. This could not be stably replicated in yeast, showing that a terminal hairpin alone is insufficient for replication, as is expected on my original model¹ which also requires specific recognition sequences for an endonuclease (or topoisomerase⁹).

Detailed study of viruses has greatly clarified the basic mechanisms of initiation and chain elongation during cellular DNA replication, because viruses often use different parts of the host cell's complex replication machinery. This may also be true for the end replication of viruses such as parvovirus and vaccinia virus that have terminal hairpins. But since other linear viruses lack hairpins and perhaps use primer proteins, there seem to be several possible mechanisms for the replication of chromosome ends, so there is no substitute for the direct study of eukaryote telomeres that Szostak and Blackburn's new cloning vector now makes possible. It will be particularly important to establish that their yeast 'telomeres', isolated by a purely functional test, really are located at chromosome ends, because unlike the 'ends' studied by Forte and Fangman⁶, they do not 'snap back' rapidly after denaturation.

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Ovarian hormones

New functions for oxytocin?

from R.B. Heap

OXYTOCIN is a hormone that has until recently been associated only with milk ejection and uterine contractions. A series of papers published last year now suggests that oxytocin also plays a part in the control of the oestrous cycle. This discovery may have important implications for contraception research.

The possibility of a wider role for oxytocin first arose in 1959 when it was shown that oxytocin hastens the onset of oestrus in cattle by shortening the life of the corpus luteum¹. Similar effects have since been described in sheep and goats^{2,3}. The hypothesis that oxytocin is involved in the regulation of luteal function is supported by both the increased release of PGF_{2 α} (which is luteolytic) from the uterus in response to oxytocin⁴ and the increase in the number of uterine oxytocin receptors that occurs towards the time of luteal regression⁵. More recently, Tony Flint at Babraham, Cambridge, has shown that the life of the corpus luteum can be prolonged in sheep by active immunization against oxytocin⁶. Measurements of the hormone in peripheral blood further indicate that levels increase with formation of the corpus luteum, and decrease at luteal regression⁷⁻⁹.

Very recently, it has been shown that the corpus luteum itself contains high concentrations of oxytocin^{10,11} and secretes it in response to PGF_{2 α} ¹². In Bristol, Claire Wathes and Ray Swann tested whether the corpus luteum of sheep contains relaxin, like that of the pigs by using a rat uterine strip in an organ bath to monitor activity in luteal extracts. However, they found that the extracts, rather than decreasing the rate of uterine contractions, which would be expected if relaxin was present, increased the contraction rate. Among possible stimulatory substances was oxytocin, and Wathes and Swann went on to show by radioimmunoassay, HPLC and bioassay that the extracts did indeed contain this hormone¹⁰. Wathes and Swann have also shown oxytocin to be present in human¹³ and bovine corpora lutea.

In experiments carried out concurrently with those at Bristol, Flint and Sheldrick found that when sheep were treated with Estrumate (Cloprostenol, ICI 80996, a potent luteolytic analogue of PGF_{2 α}) to induce luteal regression, oxytocin was released into the circulation^{12,14}. This effect could be eliminated if the sheep were ovariectomized or hysterectomized, suggesting that oxytocin is secreted by either the ovary or the uterus. These authors therefore cannulated the ovarian and utero-ovarian veins in anaesthetized sheep, and showed that the ovary can be stimulated by PGF_{2 α} (ref. 12). They have subsequently found that luteal synthesis of

oxytocin can be blocked by hysterectomy and by pregnancy, suggesting that a product of the uterus regulates oxytocin production in the corpus luteum.

Although neither the Bristol nor the Babraham group has yet isolated and sequenced luteal oxytocin, on the basis of cross-reaction with several different oxytocin antisera and evidence from physical and bioassay methods, it seems most likely that the compound is oxytocin or a very closely related peptide. These interesting observations on an ectopic site of oxytocin synthesis in a normal animal open a new era in the study of so-called neurohypophysial hormones. The only other ectopic site of synthesis of neurohypophysial hormones is the Oat cell bronchial carcinoma, which secretes arginine-vasopressin, oxytocin and their respective neurophysins¹⁵. It is interesting that other hypothalamic peptide hormones may be present in gonadal tissues — a peptide resembling luteinizing hormone-releasing hormone has recently been demonstrated in the testis¹⁶.

These findings not only question our ideas about the sites of synthesis of 'brain' hormones, but they may also be relevant to the control of luteal function in the ovary. Research groups in California¹⁷ and Brisbane¹⁸ have recently described inhibitory effects of neurohypophysial hormones, including oxytocin, on steroid synthesis in the testis and corpus luteum. The possibility arises therefore that oxytocin may be the luteolytic substance so long sought in vain in the human corpus luteum. If this is the case, its discovery in the ovary may have important consequences in contraception research. Could it be that oxytocin analogues rather than steroid derivatives offer a new form of contraception for the future? □

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