Journal of Cellular Biochemistry 58:260–267 (1995)

POU-Domain Gene Expression in the Gastrointestinal Tract

Peter J. Fuller, Dianne J. Beveridge, and Russell G. Taylor

Prince Henry's Institute of Medical Research at Monash Medical Centre, Clayton 3168, Australia (P.J.F., D.J.B.) and Department of Surgery, Royal Children's Hospital, Parkville 3052 (R.G.T.), Victoria, Australia

Abstract The process of self-renewal which occurs in the gastrointestinal epithelium is greatly amplified and accelerated during the intestinal adaptation which occurs in the residual ileum after massive small bowel resection (MSBR). As with growth and development, these processes must involve the coordinated regulation of many genes. Several families of nuclear proteins are known to be involved in the control of gene expression during development including the POU-domain genes; their expression has not been characterized in the gastrointestinal tract during normal cellular renewal or adaptation, and POU-domain encoding cDNAs were cloned from ileal RNA. Three known genes were cloned: Oct-1, Brn-1 and Tst-1 but no novel members of this gene family were identified. The encoded sequence for rat Oct-1 differs from that previously reported. Oct-1 is relatively ubiquitously expressed with increased expression during both development and adaptation. Minimal expression of Tst-1 was observed. Brn-1 exhibits limited expression in the adult gastrointestinal tract but may play a role in the fetal gastrointestinal tract.

Key words: adaptation, small bowel, gut development, homeogenes, Oct-1

The gastrointestinal epithelium is in a continuous state of growth and differentiation. Within the epithelium, a putative stem cell population gives rise to the four basic cell types: enterocytes, goblet cells, enteroendocrine cells, and Paneth cells [Podolsky, 1993]. This process of growth and differentiation is amplified during the intestinal adaptation which occurs after disease or surgery [Bristol and Williamson, 1988].

Both proliferation and differentiation demand the coordinated regulation of many specific genes. Such genes may either mediate these processes or may define the differentiated phenotype. Several large families of nuclear proteins are known to be involved in the control of gene expression during development [Kessel and Gruss, 1990]. However, limited data is available on the patterns of expression of these developmental control genes in the gastrointestinal epithelium. James and Kazenwadel [1991] have characterized the patterns of expression of homeobox genes in the adult mouse intestinal epithelium including the *caudal* family of homeobox genes whose expression is restricted to the intestine in several species [Frumkin et al., 1994]. A related family of DNA binding proteins known to be involved in the development of the neural and endocrine systems contains a novel DNA-binding motif, the POU-domain [He et al., 1989]. This family now contains over 12 members which have been classified into 5 classes [Rosenfeld, 1991].

We have recently defined the changes in gene expression occurring in the terminal ileum after massive small bowel resection (MSBR), an established animal model of intestinal adaptation [Taylor et al., 1990, 1992; Albiston et al., 1992; Fuller et al., 1993]. Increased expression of the putative enterotrophic proglucagon and peptide tyrosine tyrosine (PYY) genes are the most striking changes which occur in the residual terminal ileum post-MSBR [Taylor et al., 1990, 1992]. We sought to establish whether known or novel members of the POU-domain gene family are expressed in the gastrointestinal tract; and if they are, whether they play a role in gastrointestinal development and adaptation.

MATERIALS AND METHODS

Total RNA was prepared by the guanidinium thiocyanate/cesium chloride method [Chirgwin

Received May 12, 1994; revised August 17, 1994; accepted November 3, 1994.

Address reprint requests to Dr. Peter J. Fuller, Prince Henry's Institute of Medical Research, P.O. Box 152, Clayton, Victoria 3168, Australia.

et al., 1979] from Sprague-Dawley rats at the ages indicated. Terminal ileum was obtained both from control rats and from rats subjected to 80% small bowel resection performed as described previously [Taylor et al., 1990, 1992; Albiston et al., 1992; Fuller et al., 1993]. Female adult Sprague-Dawley rats were anaesthetized with halothane and oxygen, a midline laparotomy incision was made, and the bowel was exteriorized. Approximately 80% of the small gut was resected leaving 5 cm of jejunum distal to the ligament of Treitz and 5 cm of the ileum proximal to the ileocaecal valve. A single layer anastomosis with interrupted 6/0 prolene was then completed. Each rat served as its own control with ileal specimens taken at the lines of resection. Experimental samples were obtained from the residual bowel at least 2 cm away from the anastomosis.

The POU-domain genes were cloned by reverse transcription of the ileal RNA followed by amplification using the polymerase chain reaction (PCR) according to standard procedures [Sambrook et al., 1989]. Total RNA (2.5 μg) was reverse transcribed using AMV reverse transcriptase (Boehringer Mannheim, Sydney, Australia) and 100 pmol of the degenerate primer (5′-CCGAGCTCTCTGXCT/GXCG/TGTTG/ACAG/AAACC-3′: X corresponds to all four nucleotides) corresponding to the C-terminal amino acids of the POU-homeodomain [He et al., 1989]. POU-domain related sequences were amplified using 100 pmol of a primer immediately 5′ of the initial reverse primer (5′-CGCC-GAATTCT/GXACXACT/CTCT/CTCXAG-3′) together with 100 pmol of the forward primer (5′AGXCAA/GACXACCATCTGC/TCGXTTT/CGAA/G-3′) corresponding to the N-terminal amino acids of the POU-specific domain [He et al., 1989]. The reverse primer contained an EcoR1 restriction site (underlined) to facilitate subcloning of resultant products. Amplification was for 30 cycles with an initial denaturation step at 95°C for 5 min and subsequently for 90 s, annealing at 60°C for 120 s, and extension at 72°C for 180 s. Bands of the expected size, visualized by agarose gel electrophoresis were subcloned into pGEM series vectors (Promega, Madison, WI) for dideoxy sequencing of both strands using SP6 and T7 primers and Sequenase (USB, Cleveland, OH).

A solution-hybridization nuclease protection assay using 25 μg of total cellular RNA was performed as described by Sambrook et al. [1989] and Albiston et al. [1992]. ^{32}P-labeled single stranded probes were synthesized in the antisense orientation from linearized plasmids with SP6 RNA polymerase (POU clones) or T7 RNA polymerase (GAPDH). This 145 base rat glyceraldehyde 3-phosphate dehydrogenase (GAPDH) cRNA probe was used as a control. RNA was annealed with 1×10^5 cpm of labeled probe overnight (16 h) in buffer containing 60% formamide and then digested with 600 U of S1 nuclease (Boehringer Mannheim) for 1 h at 37°C. The digested RNA was precipitated with isopropanol and analysed by electrophoresis in a 6% acrylamide, 8.3 M urea DNA sequencing gel. After electrophoresis the gel was dried and exposed to Kodak XAR film (Eastman Kodak, Rochester, NY). POU mRNA abundance relative to control GAPDH transcripts was determined with an Olympus CUE-2 Image Analysis System (Selby Scientific, Melbourne, Australia).

RESULTS

Three previously described POU-domain genes (Oct-1, Brn-1, and Tst-1) were cloned and sequenced from rat ileum. Of the 46 PCR clones isolated and sequenced, 9 were identified as POU-domain genes. Of these, seven encoded Oct-1; with one Brn-1 and one Tst-1 clone being identified. Oct-1 clones were amplified from control ileal RNA and ileal RNA obtained 18 and 24 h post-MSBR. The Brn-1 and Tst-1 clones were both amplified from ileum 24 h post-MSBR. The predicted amino acid sequences for both Brn-1 and Tst-1 were identical to the published sequences [He et al., 1989]. The predicted amino acid sequence of rat Oct-1 (Rat-2 in Fig. 1) differs from that reported by Lillycrop and Latchman [1991] (Rat-1 in Fig. 1). These differences are unlikely to reflect Taq polymerase errors as the identical sequence is derived from seven clones from independent PCR reactions using three separate sources of RNA. Our sequence differs at 6 positions from that of Lillycrop and Latchman [1991] but is identical to the murine Oct-1 sequence and to a recently cloned rat Oct-1 cDNA [Kambe et al., 1993]. The murine sequence is derived from cDNA clones [Stepchenko, 1992; Suzuki et al., 1993]; a shorter, PCR derived sequence [Goldsborough et al., 1990] differs at residue 13 in the spacer region where an aspartate is reported rather than an alanine. Ironically, the Rat-1 sequence has an aspartate at this position [Lillycrop and Latchman, 1991]. The rodent sequences are identical

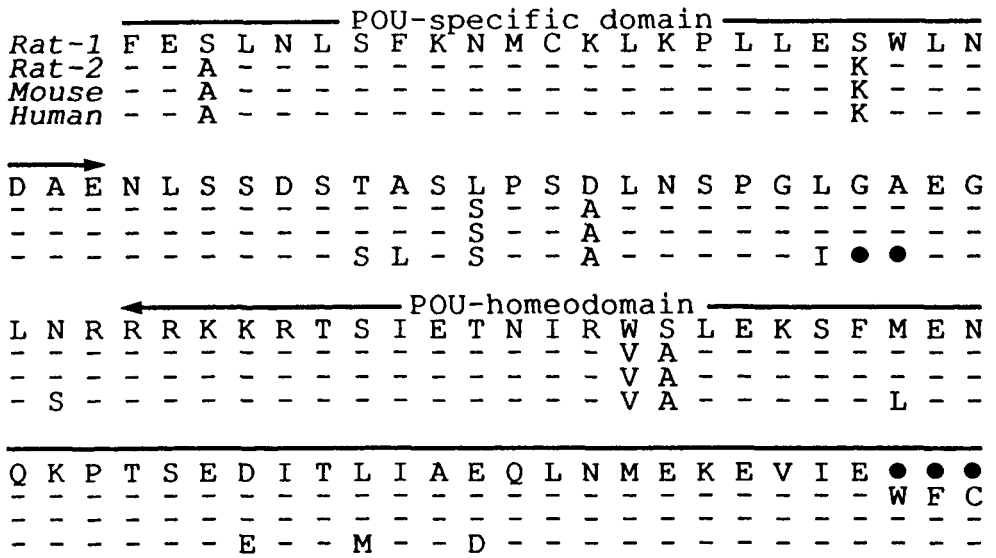

Fig. 1. Oct-1 amino acid sequences. Comparison of the published amino acid sequences for the rat (Rat-1; [Lillycrop and Latchman, 1991]), mouse [Stepchenko, 1992; Suzuki et al., 1993], and human [Sturm et al., 1988] Oct-1 POU-domains with the rat Oct-1 sequence (Rat-2) predicted from the clones isolated and reported by Kambe et al. [1993]. Conserved amino acids are indicated (−). The human sequence is 2 residues shorter in the region between the POU-specific and POU-homeodomain.

to the human sequence in the POU-specific domain but several differences occur in the POU-homeodomain. The previously reported rat sequence (Rat-1) differs in both domains from the other Oct-1 sequences, which suggests that this sequence might represent a novel POU-domain containing gene.

In order to define the patterns of expression of these three POU-domain genes in the gastrointestinal tract, S1 nuclease protection assays for each of the genes were established (Fig. 2). Protected bands of the predicted size were identified in total RNA from the control tissues (kidney and/or brain) [He et al., 1989]. The adult small bowel expressed Oct-1 (Fig. 2A) but not Tst-1 (Fig. 2B) or Brn-1 (Fig. 2C). These SI nuclease protection assays were used to examine the expression of these 3 genes throughout the gastrointestinal tract (Table I). Whilst the ubiquitous transcription factor Oct-1 exhibited widespread expression, Brn-1 expression was observed only at low abundance in the duodenum and very low abundance in the lower bowel. Tst-1 was expressed at low abundance in the corpus of the stomach and very low abundance in the large bowel. Oct-1 expression was also detected in ileum 4 days post-MSBR.

In view of the known role of these genes in the ontogeny of the nervous system [He et al., 1989; Rosenfeld, 1991], the developmental patterns of Oct-1, Brn-1, and Tst-1 expression were examined in the ileum, duodenum, colon, and kidney (Table II). The times examined were chosen to span the key events in gastrointestinal development: birth and weaning. Oct-1 shows high levels of expression at birth which fall with age in ileum, colon, and kidney. A representative autoradiographic analysis of the levels of Oct-1 mRNA in the ileum together with the results of the scanning densitometric analysis are shown in Figure 3. In the duodenum, the increase in expression of Oct-1 peaks at day 15, paralleling the increased gene expression and subsequent maturation which precedes weaning; a period of marked growth [Henning, 1985]. The level of Tst-1 expression is generally low in the kidney and is essentially absent in the gastrointestinal tract. In all tissues examined Brn-1 expression is significant at birth and falls with maturation.

Oct-1 was the only one of the 3 genes to show any expression post-MSBR (Table I). Levels of Oct-1 in control adult terminal ileum are low to undetectable but are clearly present 6 h post-MSBR. This elevation is sustained until 4 days post-MSBR when the levels start to decline. The autoradiographic analysis (Fig. 3A) of the levels of Oct-1 mRNA during development and post-MSBR are shown together with the results of a scanning densitometric analysis (Fig. 3B) in

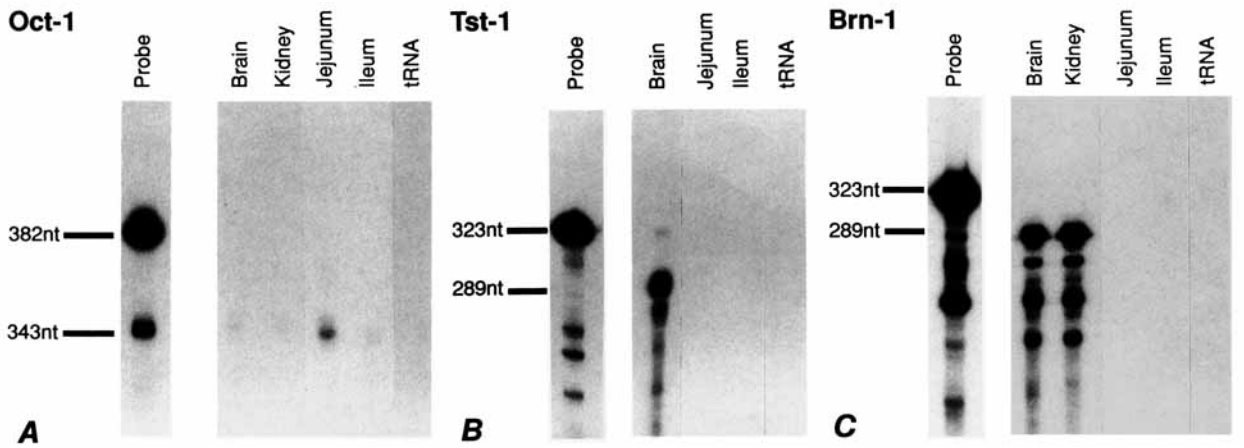

Fig. 2. S1 nuclease protection assays. Representative protection assays of 25 μg of total RNA from adult control rat brain, jejunum, terminal ileum, and, in panels A and C, kidney. Also shown is the labeled probe in the absence of S1 nuclease and with 25 μg tRNA as a negative control. The size in nucleotides of the probe and the protected fragments for the Oct-1 **(A)**, Tst-1 **(B)**, and Brn-1 **(C)** probes are indicated. The autoradiographs were exposed for 16, 7, and 16 days, respectively.

TABLE I. Tissue Distribution of POU-Domain Gene Expression*

	Brain	Testes	Kidney	Corpus	Antrum	Duodenum	Jejunum	Ileum	Ascending colon	Descending colon	Resected ileum
OCT 1	+	ND	+	++	−	+	++	+	++	++	++
BRN 1	+++	ND	+++	−	−	++	−	+/−	+/−	+/−	+/−
TstI	+++	++	+	+	−	−	−	−	+/−	+/−	−

*Relative density of signal for each probe across the tissue is indicated as follows: −, not detected; +, low; ++, moderate; +++, high; ND, not determined.

which the levels of Oct-1 mRNA are corrected for loading using the GAPDH probe.

DISCUSSION

The adult intestinal epithelium has a remarkable rate of proliferation and differentiation. The mechanisms which maintain homeostasis in this epithelial cell population have yet to be elucidated [Podolsky, 1993]. The four epithelial cell populations are derived from a single pluripotent stem cell which resides in the crypts. One lineage, the Paneth cells, migrate to the base of the crypts whilst the other three lineages (columnar, goblet, and enteroendocrine) migrate toward the villus [Podolsky, 1993]. This process of cell proliferation and differentiation is likely to be regulated by DNA-binding nuclear transcription factors. Many of these developmental control genes have been identified and appear to be members of gene families or share certain motifs [Kessel and Gruss, 1990]. A homeobox containing gene, *Cdx-1*, is expressed in murine intestinal epithelial cells [Duprey et al., 1988]. James and Kazenwadel [1991] have characterized the patterns of expression of 9 homeobox genes in adult mouse intestine. Of these homeogenes, expression of members of the *caudal* family of vertebrate homeobox genes is restricted to the intestinal epithelial. The murine *Cdx-1* and *Cdx-2* genes are expressed exclusively in the intestine with a rostrocaudal profile of expression [James and Kazenwadel, 1991; Hu et al., 1993]. The rat homolog of *Cdx-1* is also expressed preferentially in the colon [Freund et al., 1992] and Cdx-3 from the hamster is expressed in adult intestine [German et al., 1992]. In the chicken the *Cdx-A* gene is expressed in both developing and adult intestine [Frumkin et al., 1994]. Mis-expression of the homeobox gene, Hox 3.1, in transgenic mice results in altered vertebral development and also profound gastrointestinal malformations [Pollock et al., 1992]. In this study we have examined the expression of a separate gene family which also contains a homeodomain. This family of POU-domain genes was initially identified as a pituitary specific transcription factor (*P*it-1), B-cell-specific and ubiquitous octamer-binding proteins (*O*ct-2 and

TABLE II. Ontogeny of POU-Domain Gene Expression*

	Day					
	−1	1	5	15	25	A
Ileum						
Oct-1	+++	++	++	+	+/−	+/−
Brn-1	+++	++	+++	+/−	+/−	+/−
Duodenum						
Oct-1	+	++	++	+++	+	+
Brn-1	++	+++	++	+	+/−	++
Colon						
Oct-1	ND	+++	++	++	+/−	+
Brn-1	ND	ND	+++	++	+/−	+/−
Kidney						
Oct-1	++	+++	++	+	+/−	+
Brn-1	++	+++	++	++	+	++
Tst1	+/−	+/−	+/−	+/−	+/−	+/−

*Relative density of signal for a given probe and tissue is indicated as follows: −, not detected; +, low; ++, moderate; +++, high; ND, not determined.

Oct-1, respectively), and a gene regulating cell fate in the naematode, *Caenorhabditis elegans* (*U*nc-86) [Herr et al., 1988]. These proteins share a conserved domain of 150 amino acids, the so-called POU-domain [Herr et al., 1988]. Numerous additional POU-domain genes have subsequently been identified in various species [for a review see Rosenfeld, 1991]. The POU-domain contains the highly conserved POU-specific and POU-homeo domains separated by a poorly conserved spacer region of 14–25 amino acids [Rosenfeld, 1991]. On the basis of the primary sequence in these domains the POU-domain proteins have been classified into 5 groups [Rosenfeld, 1991]. Most attention has focused on the role of these genes in neural, endocrine, and gonadal development as well as on their expression in the adult brain. POU-domain genes have not previously been described in the gastrointestinal tract. In view of the expression of homeobox genes in gastrointestinal tissues [Duprey et al., 1988; James and Kazenwadel, 1991; Hu et al., 1993; Frumkin et al., 1994; Freund et al., 1992; German et al., 1992], we hypothesised that POU-domain genes may also be expressed. Since increased proliferative activity occurs during intestinal adaptation, we speculated that POU-domain gene expression may be enhanced. Our studies of the molecular events in intestinal adaptation have focused on the enteroendocrine L-cells [Taylor et al., 1990, 1992; Fuller et al., 1993]. Given the key role of the Pit-1 and Brn-2 genes in the regulation of, respectively, prolactin/growth hormone and corticotropin-releasing hormone gene expression [Rosenfeld, 1991], we considered that one of the POU-domain genes may regulate the increased proglucagon and PYY gene expression observed in L-cells post-MSBR.

Although three known POU-domain genes were cloned from adult rat ileal RNA we failed to identify any novel members of this gene family using a PCR-based strategy which has been used successfully in studies of other tissues [He et al., 1989; Lillycrop and Latchman, 1991; Goldsborough et al., 1990]. The rat homologue of the ubiquitous transcription factor Oct-1 has been cloned. The Oct-1 protein regulates generally active genes containing an octamer sequence motif [Sturm et al., 1988] and also appears to exert important functions in DNA replication [Rosenfeld, 1991]. The amino acid sequence deduced from the seven clones isolated differs from that previously reported by Lillycrop and Latchman [1991]. Our sequence is, however, identical to the murine sequence [Stepchenko, 1992; Suzuki et al., 1993] and also to a recently published complete cDNA sequence for rat Oct-1 [Kambe et al., 1993]. The Rat-1 sequence [Lillycrop and Latchman, 1991] was cloned using PCR from immortalized primary rat sensory neurones and differs at 6 positions from the rat Oct-1 sequence [Rat-2; Kambe et al., 1993]. This sequence does not correspond to any of the other characterized POU-domain genes [Rosenfeld, 1991] so its significance is uncertain. It may be a novel but closely related member of the class II genes. The two residues which differ in each of the conserved domains in Rat-1 are also seen in other POU-domain genes at those positions [Rosenfeld, 1991]. The rodent Oct-1 sequences differ from the human sequence in the spacer region and more importantly in the POU-homeodomain but not the POU-specific domain. Of the 4 differences between the rodent and human Oct-1 POU-homeodomain sequences, two are identical to those in the human and mouse Oct-2 homeodomains. Suzuki et al. [1993] have suggested that the murine Oct-1 homeodomain is a composite of the human Oct-1 and Oct-2 sequences which may reflect host-specific differences in protein-protein interactions.

Oct-1 is known to be expressed in a range of tissues [Sturm et al., 1988; Suzuki et al., 1993]. The finding of Oct-1 expression throughout the

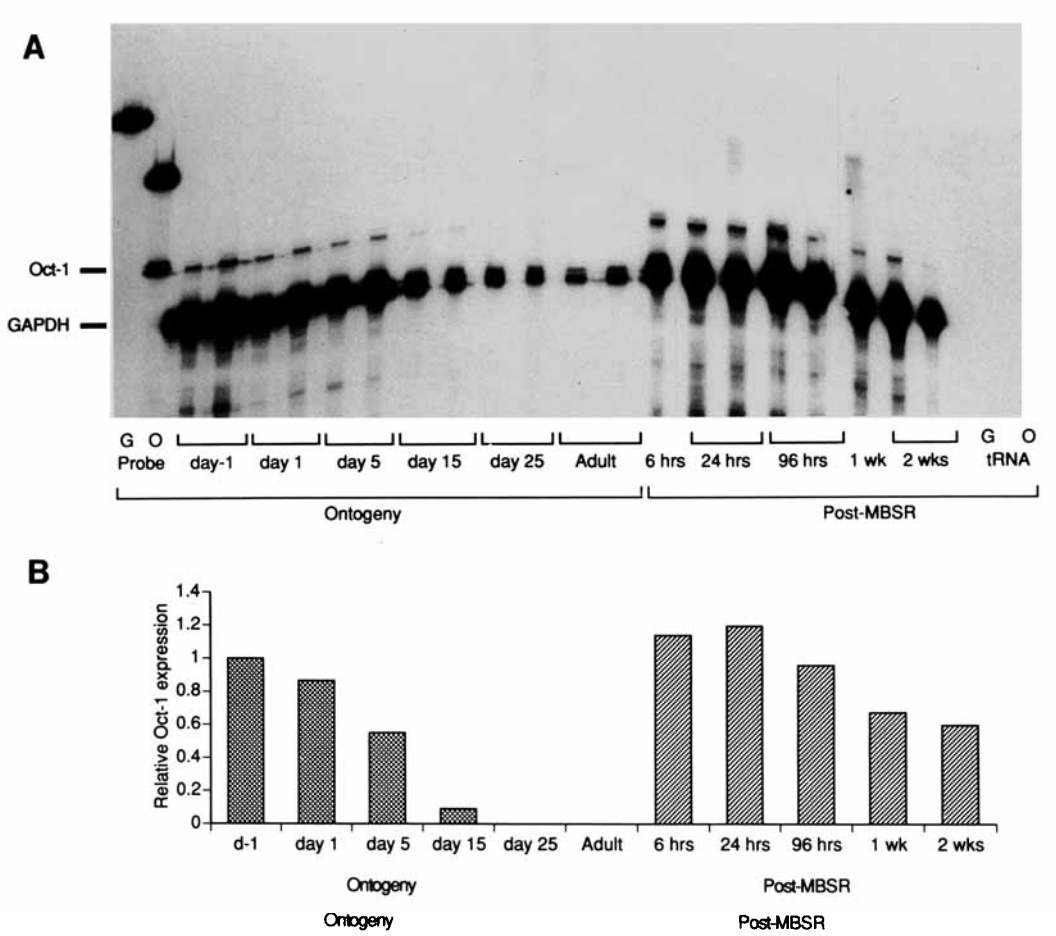

Fig. 3. Oct-1 gene expression during ileal ontogeny and adaptation. **A:** S1 nuclease protection assay with the ^{32}P labeled Oct-1 and GAPDH probes with 25 μg of total ileal RNA from rats at the ages indicated (see also Table II) and at 6, 24, 96 h, and 1 and 2 weeks post-MSBR. Also shown are the labeled probes in the absence of S1 nuclease and with 25 μg of tRNA instead of total RNA as a negative control. The positions of the protected bands with each probe is indicated. The autoradiograph was exposed for 7 days. **B:** The levels of Oct-1 mRNA expressed as a ratio with the levels at day 1 have been normalized by correction with the GAPDH probe.

gastrointestinal tract is therefore not surprising. The lack of antral Oct-1 gene expression may reflect a lower rate of proliferative activity in this part of the rat stomach. In the ileum, colon, and kidney, the highest levels of Oct-1 were observed at birth. This suggests that Oct-1 may be involved in the fetal development of these organs with a much less prominent role in the adult. This pattern of expression contrasts with that in the duodenum where levels peak at day 15. This is a period of increased cell proliferation, enhanced polyamine production and an array of enzyme changes [Taylor et al., 1992; Henning, 1985]. These changes are most marked in the duodenum and upper small bowel where they are temporally coordinated with the process of spontaneous weaning [Henning, 1985]. The increase in Oct-1 expression appears slightly ahead of enzymatic changes such as the appearance of jejunal sucrase activity [Henning, 1985]. These enzyme changes are due to the replacement of the existing epithelial cells by a new population emerging from the proliferative pool in the crypts [Henning, 1985]. It is tempting to suggest a role for Oct-1 in the changes in cell cycling which must underlie the expression of this ontogenic program. Similarly the acute increase in expression of Oct-1 in the ileum post-MSBR may be linked to increased cellular proliferation within the stem cell population in the crypts. It would be of considerable interest to determine the cellular localization of the Oct-1 expression post-MSBR.

Tst-1 which is also known as Scip or Oct-6 is a member of the third class of POU-domain proteins. Tst-1 mRNA is found in a subset of neu-

rones, oligodendroglia, specific layers of the cerebral and cerebellar cortices, Schwann cells, and in the testis. It is also expressed early in development in the inner cell mass of mouse embryos [He et al., 1989; Rosenfeld, 1991]. Tst-1 expression is very low in the gastrointestinal tract. In so far as it is present, this probably reflects expression in some component of the peripheral nervous system innervating the gastrointestinal tract.

Brn-1 is also a member of the third class of POU-domain proteins [Rosenfeld, 1991]. As the name implies, studies of Brn-1 expression have focused on the developing nervous system. Brn-1 is expressed in most regions of the cerebrum and cerebellum; this expression is correlated with the establishment of cortical lamination [He et al., 1989; Rosenfeld, 1991]. Little is yet known of the function of Brn-1. Though the levels of Brn-1 expression are low in the adult tissues examined and unaffected by intestinal adaptation, the levels of expression at birth suggest a significant role in late fetal development. As with the other two genes studied, the cellular source of the expression is of considerable interest in this first demonstration of Brn-1 expression in an epithelium. Alternatively it may be a reflection of growth and maturation in the peripheral nervous system. Its presence in both neonatal kidney and intestine as well as the relatively high levels of neonatal expression argue for an epithelial source. As with the Oct-1 expression it remains possible that POU-domain gene expression in the gastrointestinal tract is not epithelial in origin; precise cellular localization will require either hybridization histochemistry perhaps using in-situ PCR or immunohistochemistry when the appropriate reagents become available.

The demonstration of POU-domain gene expression in the gastrointestinal tract suggests that this family of nuclear proteins has a developmental role outside of the nervous system and the gonads. The high levels of expression of Oct-1 and Brn-1 at birth would suggest that further studies should be directed at elucidating the cellular and temporal patterns of their expression in the fetal intestine. In addition, it is possible that a further search for POU-domain gene expression, using the same primers but starting with fetal/neonatal tissue rather than adult tissue, may demonstrate expression of other members of the family in the developing gastrointestinal tract.

ACKNOWLEDGMENTS

We thank Mrs. Claudette Thiedeman and Ms. Sue Panckridge for assistance in preparation of the manuscript, Ms. Karen Verity for carefully reading the manuscript, and Dr. Anthony Albiston for advice on the nuclease protection assays. This work was supported by the Royal Children's Hospital Research Foundation and the Wellcome Trust through an Australian Senior Research Fellowship (P.J.F.).

REFERENCES

Albiston A, Taylor RG, Beveridge DJ, Herington AC, Fuller PJ (1992): Divergent IGF-1 and IGFBP-3 gene expression after small bowel resection: A novel mechanism to amplify IGF action? Mol Cell Endocrinol 83:R17–R20.

Bristol JB, Williamson RCN (1988): Mechanisms of intestinal adaptation. Pediatr Surg Int 4:233–241.

Chirgwin JM, Przybyla AE, MacDonald RJ, Rutter WJ (1979): Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. Biochemistry 18: 4294–4299.

Duprey P, Chowdhury K, Dressler GR, Balling R, Simon D, Guenet J-L, Gruss P (1988): A mouse gene homologous to the Drosophila gene *caudal* is expressed in epithelial cells from the embryonic intestine. Genes Dev 2:1647–1654.

Freund J-N, Boukamel R, Benazzouz A (1992): Gradient expression of *Cdx* along the rat intestine throughout postnatal development. FEBS Lett 314:163–166.

Frumkin A, Pillemer G, Haffner R, Tarcic N, Gruenbaum Y, Fainsod A (1994): A role for *CdxA* in gut closure and intestinal epithelia differentiation. Development 120:253–263.

Fuller PJ, Beveridge DJ, Taylor RG (1993): Ileal proglucagon gene expression: Characterisation in intestinal adaptation using in situ hybridization. Gastroenterology 104: 459–466.

German MS, Wang J, Chadwick RB, Rutter WJ (1992): Synergistic activation of the insulin gene by a LIM-homeo domain protein and a basic helix-loop-helix protein: Building a functional insulin minienhancer complex. Genes Dev 6:2165–2176.

Goldsborough A, Ashworth A, Willison K (1990): Cloning and sequencing of POU-boxes expressed in mouse testis. Nucleic Acids Res 18:1634.

He X, Treacy MN, Simmons DM, Ingraham HA, Swanson LW, Rosenfeld MG (1989): Expression of a large family of POU-domain regulatory genes in mammalian brain development. Nature 340:35–42.

Henning SJ (1985): Ontogeny of enzymes in the small intestine. Ann Rev Physiol 47:231–245.

Herr W, Sturm RA, Clerc RG, Corcoran LM, Baltimore D, Sharp PA, Ingraham HA, Rosenfeld MG, Finney M, Ruvkun G, Horvitz HR (1988): The POU domain: A large conserved region in the mammalian *Pit-1, Oct-1, Oct-2* and *Caenorhabditis elegans* unc-86 gene products. Genes Dev 2:1513–1516.

Hu Y, Kazenwadel J, James R (1993): Isolation and characterization of the murine homeobox gene *Cdx-1*. J Biol Chem 268:27214–27225.

James R, Kazenwadel J (1991): Homeobox gene expression in the intestinal epithelium of adult mice. J Biol Chem 266:3246–3251.

Kambe F, Tsukahara S, Kato T, Seo H (1993): The POU-domain protein Oct-1 is widely expressed in adult rat organs. Biochim Biophys Acta 1171:307–310.

Kessel M, Gruss P (1990): Murine development control genes. Science 249:374–379.

Lillycrop KA, Latchman DS (1991): Cloning and sequencing of the rat Oct-1 POU box. Nucleic Acids Res 19:3744.

Podolsky DK (1993): Regulation of intestinal epithelial proliferation: A few answers, many questions. Am J Physiol 264:G179–G186.

Pollock RA, Jay G, Bieberich CJ (1992): Altering the boundaries of Hox3.1 expression: Evidence for antipodal gene regulation. Cell 71:911–923.

Rosenfeld MG (1991): Pou-domain transcription factors: Pou-er-ful developmental regulators. Genes Dev 5:897–907.

Sambrook J, Fritsch EF, Maniatis T (1989): "Molecular Cloning: A Laboratory Manual." 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Stepchenko AG (1992): The nucleotide sequence of mouse Oct-1 cDNA. Nucleic Acids Res 20:1419.

Sturm RA, Das G, Herr W (1988): The ubiquitous octamer-binding protein Oct-1 contains a POU domain with a homeobox subdomain. Genes Dev 2:1582–1599.

Suzuki N, Peter W, Ciesiolka T, Gruss P, Schöler HR (1993): Mouse Oct-1 contains a composite homeodomain of human Oct-1 and Oct-2. Nucleic Acids Res 21:245–252.

Taylor RG, Verity K, Fuller PJ (1990): Ileal glucagon gene expression: Ontogeny and response to massive small bowel resection. Gastroenterology 99:724–729.

Taylor RG, Beveridge DJ, Fuller PJ (1992): Ileal glucagon and peptide YY gene expression: Response to inhibition of polyamine synthesis in the presence of massive small bowel resection. Biochem J 286:737–741.