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Functional development of the meso- and metanephros

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Abstract This review highlights the important roles the mesonephros may play in development. In the ovine fetus it is an excretory and endocrine organ and may contribute to the formation of normal gonads and adrenals. The metanephros of the ovine fetus has the important function of providing large quantities of dilute urine for the maintenance of amniotic and allantoic fluid volumes, essential for normal placentation and development.

Key words Mesonephros · Metanephros · Nephrogenesis · Renin-angiotensin

Introduction

Functioning kidneys are essential for life after birth and, although the fetus can survive without kidneys (renal agenesis), development is compromised. There are many reasons why the study of kidney development is important. Recently it has been proposed that many disease states of the adult, including hypertension and kidney disease, may be determined by events that occurred during fetal development [1]. Maternal treatment with some drugs (such as angiotensin converting enzyme inhibitors) can alter fetal kidney function and cause developmental abnormalities. Babies that are growth retarded may have small kidneys, even when corrected for body weight, which may in later life compromise renal function [2]. This makes it very important to understand normal kidney development and identify factors that may influence renal growth and functioning.

The fetal metanephric kidney produces a large volume of dilute urine which is a major input into the amniotic fluid [3]. The amniotic fluid is essential as an aqueous environment, for the symmetrical growth of the fetus, and correct lung development. Any factor that prevents urine being produced by the kidneys could result in lack of amniotic fluid and subsequent fetal growth deformities. In addition, the kidney produces hormones, some of which may act locally and some that affect other developing organs or systems.

This review examines the normal growth and function of the mammalian meso- and metanephros. There have been a number of recent reviews describing the morphological development of the metanephros and factors important for correct structural formation [3–6]. This review shall focus more on mesonephric development and functions of the mesonephros and metanephros in the fetus. Information from the human is described where available, but most experimental studies examining function have been conducted on the fetal lamb or the fetal and neonatal mouse. The fetal sheep provides a good model for many aspects of nephrogenesis, because the timing and development of each set of kidneys is similar to the human (Table 1). Thus, much of the work described in this review is from studies in the chronically cannulated ovine fetus.

Nephrogenesis – an overview

During embryonic and fetal development in mammals, there are three different pairs of renal organs. The first two, the pronephros and the mesonephros, exist, in most cases, for defined periods of intrauterine development. These organs regress and the third organ, the metanephros, becomes the permanent adult kidney [3]. The pronephros is the most primitive and is not thought to be functional in mammals during embryogenesis. The mesonephros is a functional kidney in some species, but the tubules lack a loop of Henle.

The metanephros, which becomes the permanent adult kidney, first appears some time after the mesonephros, but for a period of gestation the two sets of kidneys co-exist. Development of each set of kidneys is considered below.

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Table 1 Meso- and metanephric development in different species. Post-partum (pp)

Species	Length of gestation	Mesonephric development	Percentage gestation	Metanephric development	Percentage of gestation
Human	40 weeks	4–16	10–40	5–36.5	12–90
Sheep	145–152 days	17–57	11–38	27–135	18–90
Pig	112–114 days	15–24	9–21	20-pp3	19–118
Mouse	20 days	10–13	53–70	11-pp3	55–113
Rat	21 days	12–17	57–81	12-pp8	57–138
Elephant	92 weeks	<13–>24	<14–>26	14–?	15–?
Native cat	21 days	–pp30	–240	pp2–pp89	110–520

The pronephros

In mammals, the pronephros is quite rudimentary and non-functional, but in many lower vertebrates, such as amphibia and fish, the pronephros acts as the embryonic kidney and is essential for survival [7]. In the pronephros, after filtration through the glomus, fluid enters the coelomic cavity also known as the nephrocoel. From there the filtrate is collected via ciliated funnels (nephrostomes) that are connected to the pronephric tubules. Surrounding these tubules is a blood sinus into which reabsorbed fluid passes, whilst unabsorbed fluid is excreted via the pronephric (Wolffian) ducts. The sheep does not develop a pronephros as such, but does form a giant glomerulus at the cranial end of the future mesonephros [8]. Many genes known to be critical for meso- and/or metanephric induction are also expressed by the pronephros. The expression patterns of these genes in the pronephric kidney is similar to that observed in the meso- and metanephros, suggesting a role for these genes in the growth and development of all three kidney types [7].

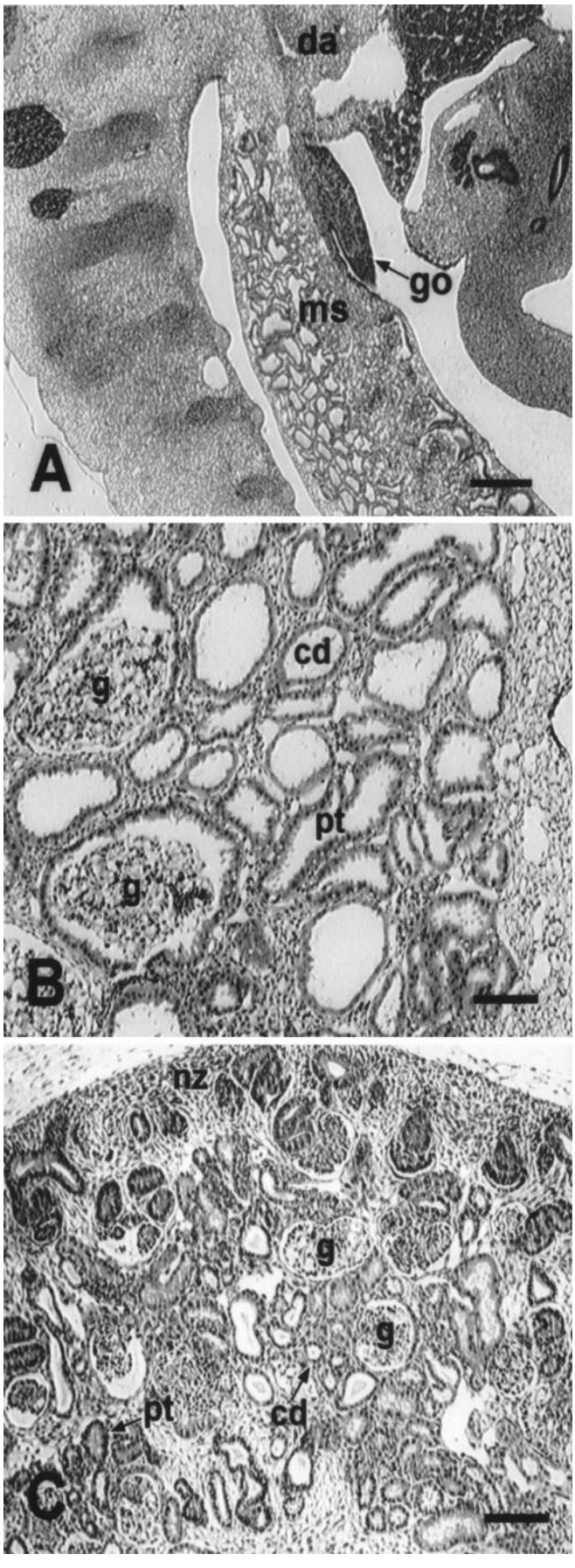
The mesonephros

In the human embryo at day 24–26, mesonephric ducts form on the lateral and ventral sides of the nephrogenic ridge and induce formation of the mesonephros [9]. By day 28, these ducts join the cloaca and by 8 weeks post conception, the human mesonephros has reached maximal size and starts to regress. Complete regression occurs by week 16 [10]. Although present in most other animals, it is interesting to note that mesonephric development and complexity varies significantly between species (Table 1). In some species the mesonephros appears to have an excretory capacity, whilst in others is clearly non-functional. The mesonephros of the sheep [11] exists for a very similar period of gestation to that of the human, whereas the rodent mesonephros is present much later and for a shorter period of gestation [12]. Generally, the glomeruli of the mesonephros are relatively large compared with those of the metanephros (Fig. 1B, C) but there are many fewer of them (between 10 and 50 per kidney). Several marsupial species have been well studied as the young are born with only a mesonephros present, and in these species the mesonephros is present for a significant time after birth [13]. The elephant fetus, which has a gestation of 22 months, has a mesonephros containing nephrostomes. As described above, these are ducts that connect the coelomic cavity with the renal glomeruli and were thought to exist only transiently in the cranial portion of the mesonephros before glomeruli formation. Their presence throughout mesonephric growth and degeneration may reflect the elephant's aquatic ancestry [14]. In both the mouse and rat [15], as well as chick [16], the cranial and caudal nephrons of the mesonephros have been shown to vary in both morphology and gene expression, suggesting that regulation of development may differ from the two parts of the mesonephros. An example of this is seen in mice that are null mutant for the Wilms tumor gene product (WT-1). These mice develop cranial mesonephric tubules but not caudal tubules [15].

The metanephros

The metanephros, which is the permanent kidney in mammals, begins formation as a budding from the caudal end of the mesonephric duct (for detailed description of human nephrogenesis see [10]). This first event requires an induction signal from the surrounding metanephric mesenchyme. Although the signal(s) have not been clearly elucidated, it has been shown that ureteric bud cells contain receptors for a number of growth factors. After the ureteric bud has formed, reciprocal inductive interactions occur. The ureteric bud causes the metanephric mesenchyme to differentiate and form nephrons, whilst the metanephric mesenchyme causes the ureteric bud to grow and bifurcate to form collecting ducts. The differentiation of the metanephric mesenchyme involves at least two components: apoptosis is stopped and the metanephric mesenchyme differentiates into stem cells at the periphery of the kidney, which forms the nephrogenic zone and which can then epithelialize [4].

The ureteric bud dilates at its growing tip and forms an ampulla. Cells from the nephrogenic ridge cluster around this ampulla and are known as the metanephric cap or blastema. Induction signals from the ampulla cause the metanephric blastema to condense and form a closed tube of epithelial cells, the nephrogenic vesicle. This becomes a rounded structure and the cells proliferate to form a comma- and then S-shaped body. The ureteric bud undergoes a series of divisions in which the ampulla divides with one part going to induce a nephrogenic vesicle and the other to divide again. By this pro-



cess, many hundreds of thousands of nephrons may be formed [4]. Nephrogenesis is complete before birth in human and sheep, but not in many other species (Table 1).

Many gene products have been implicated in metanephric development and well reviewed in recent years [3–6]. These include a wide variety of growth factors (GF) and their receptors (insulin-like, epidermal, transforming, nerve, hepatocyte, fibroblast, platelet-derived, and vascular-endothelial GFs, bone morphogenetic proteins, leukocyte inhibitory factor), proto-oncogenes, transcription factors, and suppressor genes (n-*myc*, *PAX2* and *8*, *WT1*, *Lim 1*, *Wnt 4*, *bcl 2*, hepatocyte nuclear factor), extracellular matrix (ECM) components and degrading enzymes (collagen, fibronectin, tenascin, proteoglycans), and ECM ligands and receptors (integrins, cell adhesion molecules). There appears to be a certain degree of redundancy in that some factors identified during in vitro studies as being of crucial importance in normal development do not cause abnormalities when the gene is knocked-out in vivo [17].

As the ureteric bud branches from the Wolffian duct and is the source of the inducers of metanephric mesenchyme condensation, no metanephros forms without mesonephros and Wolffian duct formation first. However, so far only a few genes have been studied specifically in mesonephric development. Abnormalities occur when the *PAX-2* or *Lim 1* gene has been "knocked-out" (no mesonephros formation) or the *WT1* gene is deleted (abnormal mesonephros forms [7]). Metanephric kidneys with serious morphological and functional deficits occur in the absence of a normal functioning renin-angiotensin system (RAS) [12], or one prostaglandin-synthesizing enzyme – cyclo-oxygenase 2 [18].

Possible functions of the mesonephros (Table 2)

Excretion

The ability of the mesonephros to function as an excretory organ in some species may be related to the type of placentation. Those species with a more-primitive placenta (such as the pig and sheep) have the most highly developed mesonephros [19]. Ovine fetuses can produce a hypotonic urine from day 18 of gestation. This urine passes via the urachus into a second fluid-filled sac, the allantois. The allantoic fluid in ovine fetuses at 20 days of gestation is approximately 3 ml, but by day 24 there is 20 ml of fluid (E.M. Wintour, unpublished observations), suggesting the mesonephros has a well-developed excretory capacity by 3 weeks of gestation. Expansion of the

Fig. 1 **A** The ovine fetus at 27 days' in the region of the dorsal aorta (*da*), gonad (*go*), and mesonephros (*ms*). Note the association between the gonad and mesonephros, ×40, *bar*=250 μM, **B** Ovine mesonephros and **C** metanephros at 41 days', ×100, *bar*=100 μM. Note the difference in size of glomeruli (*g*). *pt*, Proximal tubule; *cd* collecting duct; *nz*, nephrogenic zone

Table 2 Features of the mesonephros

Structural features	No loops of Henle Small number of relatively large glomeruli
Species variations	Permanent kidney of fish Variable complexity: pig>sheep>human>rat Present at different gestational periods (see Table 1)
Excretory function	Present in some species – sheep, pig – where fluid contributes to allantoic fluid
Genes expressed	Erythropoietin, Na/K ATPase, calbindin D28K, growth hormone receptor, renin, angiotensin converting enzyme, angiotensinogen, AT1 and AT2 receptors, WT-1, PAX-2 and 8
Other possible functions	Role in gonad and adrenal development

allantoic membrane is important for establishing contact between fetal blood vessels and the maternal uterine circulation at specific sites, known as caruncles. Thus mesonephric function is important for initial placentation in sheep.

Erythropoiesis

In the primitive embryo there is a region termed the AGM – the region of the dorsal aorta, gonad, and mesonephros (Fig. 1). An interesting study has recently identified this area as the source of definitive hematopoiesis, i.e., the pre-liver site of hematopoietic activity [20]. The mesonephros is known to be the site of erythropoiesis in the fish (where it is the permanent kidney) and the gene for erythropoietin (EPO) is expressed in ovine mesonephros [21, 22].

Contribution to gonad and adrenal

In the development of the ovary and testis, cells of the mesonephros clearly play a part [19]. The gonad begins formation as a thickening in the middle of the nephrogenic ridge. This “genital ridge” becomes elongated and covered with coelomic epithelium and soon develops a longitudinal duct lateral to the mesonephric duct. Nearly 20 years ago Zamboni et al. [23] observed in the sheep fetus that at day 24–29 post conception cells from the cranial third of the mesonephros migrated outside the glomerulus and formed clusters. These clusters were observed all the way into the genital ridge and became associated with primordial germ cells. After sexual differentiation at 31 days’ in the female fetus, the movement of cells became more organized and pronounced, such that a compact mass of cells extended from the mesonephros into the ovary. The cell mass then breaks up and associates with germinal cells.

In the male, although development of the testis can occur in the absence of the mesonephros, many cords fail to differentiate correctly [24]. These authors showed in isolated tissue that from day E11.5 cells migrate into the differentiating testis from the mesonephric region. If the mesonephros was removed or separated by a filter from the testes, then normal cords did not form.

Cells of the mesonephros may also be involved in growth of the adrenal gland. Morphological studies indicate that cells from the mesonephros migrate into the adrenal cortex [25]. It has also been proposed that a unique population of mesenchymal cells gives rise to both the gonad and adrenal [26].

Role in limb development

It has been proposed that the mesonephros is important for limb development in the chick [27]. In particular, it was thought that fibroblast-growth factor 8 (FGF-8) produced in the mesonephros induced wing budding [28]. However, this has now been disproved by elegant studies from Fernandez et al. [29]. They were able to block development of the mesonephros by mechanical arrest of the caudal extension of the Wolffian duct. The mesoderm in the mesonephric area did not express the FGF-8 gene, but limb development was completely normal. This is a good example of how careful one must be in the interpretation of the functional consequences of gene localization studies.

Endocrine function

The mesonephros expresses the gene for erythropoietin and all components of the RAS, as detailed later.

Special features of metanephric function in utero

The urine produced by the fetus is an important component of amniotic fluid and any factor that alters fetal urine production in the long term can seriously affect amniotic fluid volume. Recent studies show that bilateral nephrectomy in the ovine fetus at 100 days’ results in some changes in fetal plasma composition over the 2 weeks following nephrectomy. Fetal plasma chloride decreased, whilst phosphate, magnesium, and creatinine increased (Fig. 2).

Metanephric function in the fetus differs from that in the adult in that there is a lower glomerular filtration rate (GFR) (approximately half that of the adult) and renal blood flow is only 3% of cardiac output, compared with 25% in the adult [30]. By mid-gestation in the sheep, it is possible to chronically cannulate the fetal bladder. Basal urine flow rate at this age (75 days’) is 5–6 ml/h, even

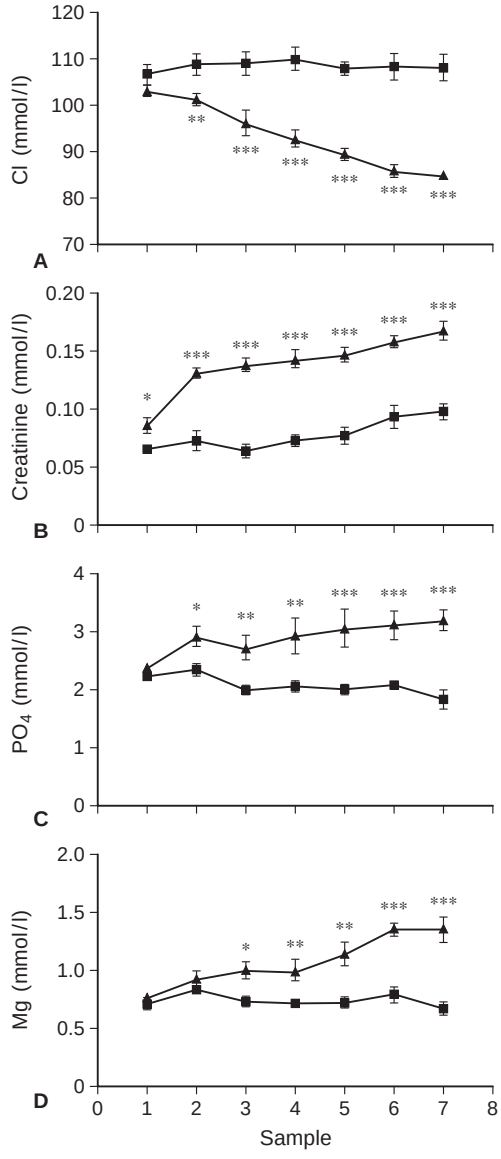


Fig. 2 Changes in: **A** chloride (*Cl*), **B** creatinine, **C** phosphate (PO_4), and **D** magnesium (*Mg*) in ovine fetal plasma for 2 weeks following nephrectomy. Numbers represent time after surgery: 1=4 h, 2=48 h, 3=4 days, 4=7 days, 5=9 days, 6=11 days, and 7=14 days. *Squares* indicate control (intact) fetuses, *triangles* represent fetuses which had undergone bilateral nephrectomy. **P*<0.05, ***P*<0.01, ****P*<0.001

though the fetus only weighs 150–250 g. This equates to nearly 0.5 l urine/kg body weight per day, which in an adult would clearly represent a case of diabetes insipidus. The urine during development is always hypotonic unless the fetus is severely stressed [3]. The production of a relatively large volume of hypotonic urine is essential for normal fetal fluid maintenance. It is possible for the fetus to maintain this urine flow because: (1) the kidney is relatively insensitive to arginine vasopressin (AVP) and (2) AVP release is relatively insensitive to osmotic stimulation [31]. The relative insensitivity to AVP reflects to some extent low expression of the gene encoding the water channel, aquaporin 2 (AQP 2), rather than a lack of functioning V2 receptors.

AQPs are a recently cloned family of specific water channels. AQP 1 is the water channel found in the proximal tubules and in the thin descending limb of the loop of Henle [3]. The expression of the gene for AQP 1 can be detected in the metanephric kidney of ovine fetuses from 41 days of gestation, but not in the mesonephros at this time [32]. Gene expression increased sevenfold from 60 to 140 days of gestation and reached adult levels by 6 weeks after birth [33]. Dexamethasone treatment for several days at mid-gestation, previously shown to accelerate morphological development [34], also increased AQP 1 expression at this time. In the human fetus, AQP 1 is seen in the metanephros from week 15 of gestation and AQP 2 from as early as week 12 [35].

Urine cannot be concentrated unless the specific water channels, encoded by the *AQP 2* gene, are present on the apical surface of the principal cells of the cortical and medullary collecting ducts. The gene for AQP 2 is regulated by AVP and is expressed in the ovine fetal kidney, where mRNA can be detected by polymerase chain reaction from about 40 days of gestation in the metanephros. Levels increase over gestation, however they are only 5% of adult levels at mid-gestation and 41% of adult levels by term (E.M. Wintour, unpublished observations). The slow acquisition of these water channels accounts for some of the insensitivity to AVP.

In the ovine fetus during the last third of gestation, stress, such as hemorrhage or hypoxia, will cause release of AVP, which will decrease urine flow rate and can cause the urine to become hypertonic. The maximal urinary osmolality, however, is much less than in the adult [36]. Many other factors have been identified to increase urine flow. Despite the very high urine flow, flow rate can actually be increased without affecting osmolality, three- to fivefold by high levels of glucocorticoids, angiotensin II, or atrial natriuretic peptide during the last third of gestation [4, 36].

Development of metanephric endocrine function

The kidney, in addition to its excretory function, is an important endocrine organ in utero. Major hormones produced by the kidney include EPO and the metanephros also expresses components of the RAS. Thus angiotensin II can be produced locally and may have effects on development and function of the metanephros.

Erythropoietin

Although the kidney has long been recognized as the major site of EPO production in the adult, for many years the liver was thought to be the predominant site of production in the fetus, at least until close to term. However, recent molecular and hybridization histochemistry studies have demonstrated that the EPO gene is expressed

strongly in the meso- and metanephros from as early as 40 days of gestation in the sheep [21]. In fact, metanephric expression of the EPO gene was highest from 60–100 days of gestation and declined markedly close to term. At all ages, in both the meso- and metanephros, EPO mRNA was expressed in interstitial cells in the vicinity of the proximal tubules. Metanephric expression of the EPO gene can be altered by changes in glucocorticoid status, with dexamethasone or cortical infusions causing a significant decrease in expression in the first two-thirds of gestation, whilst adrenalectomy caused an increase close to term [21]. It is interesting that neonates with some congenital kidney diseases have normal EPO production and some infants with renal agenesis actually have elevated serum EPO concentrations. This may indicate that the liver is able to compensate for the lack of kidney EPO production under normal circumstances. In ovine fetuses that had been nephrectomized at 100 days of gestation (term=150 days), basal EPO concentrations were maintained for 2 weeks, although levels did not increase with the onset of hypoxia (K.M. Moritz, E.M. Wintour, unpublished observations). When nephrectomized fetuses hemorrhaged, liver expression of the EPO gene only increased to the same degree as in intact hemorrhaged fetuses, suggesting the liver is unable to compensate in times of hemorrhagic stress.

Renin-angiotensin system

The RAS is present and active during fetal life. It is thought that the major role of this system in the fetus is to maintain fetal GFR and ensure that large volumes of urine are produced [30]. Evidence for this comes from a wide range of animal experiments and clinical studies [12]. Much of the work in this area has been done in the developing rat kidney [37], but there is now recent evidence from the human and sheep. Knock-out studies in mice have also implicated the RAS as being necessary for the normal growth and development of the metanephric kidney.

Although the RAS operates systemically, the kidney is able to produce all components of the system and thus the local (intra-renal) production of angiotensin II may be very important. Renin mRNA can be detected in the human mesonephros at about 30 days of gestation [38] and in the sheep from at least 40 days'. Expression is first observed in blood vessels outside the kidney and then becomes more widespread throughout the renal arterial vasculature. In the metanephros, renin is first reported in the human at 56 days' and the sheep at 41 days' [38, 39]. A similar profile of expression is seen for angiotensinogen, which is first observed in proximal tubules of the human mesonephros at 25–30 days of gestation and in the metanephros from 56 days'. The mRNA for angiotensin converting enzyme is also detected in the meso- and metanephros of the human and sheep from very early in gestation in proximal tubules and collecting ducts [39]. Finally, the developing meso- and metanephros express the genes for both the angiotensin type 1 and 2 receptors. In the ovine fetus, both receptor types are present in the mesonephros at 27 days of gestation and in the meso- and metanephros at 41 days' [40]. Throughout gestation, the angiotensin 1 (AT1) receptor was located in developing glomeruli as well as in the medulla and medullary rays (when present). At 41 days of gestation, the AT2 receptor was expressed in interstitial cells of the metanephros around the comma- and S-shaped nephron structures. By 75 days' it was possible to clearly identify the AT2 mRNA in the macula densa, a specialized part of the distal tubule close to the glomerulus. Expression of the AT2 receptor declined towards term and was absent in the 2-day lamb kidney.

Expression of all components of the system from very early in gestation means angiotensin II, produced locally in the kidney, could influence renal development and function from this very early stage. What may be the role of angiotensin II in early kidney development? Some information can be gained from studies where the system has been altered. Interesting abnormalities have been observed in mice in which the gene for one part of this system has been knocked-out. Mice that lack the gene for angiotensinogen show delayed glomerular maturation and develop lesions in the renal cortex [41], whilst angiotensin converting enzyme knock-out mice have distorted renal vasculature along with greatly increased levels of renin gene expression, and both have hypoplastic papillae [42]. In the mouse there are two subtypes of the AT1 receptor, namely the AT1a and the AT1b, and if either subtype is knocked-out individually, there do not appear to be any kidney abnormalities [43, 44]. However, in double-mutant mice (i.e., those null mutant for both the 1a and 1b receptors), there are grossly abnormal kidneys, similar to those seen in the angiotensinogen knock-out mice [45].

The level of expression of the RAS may also be crucial for normal development. Babies that have high cord renin concentrations have significantly smaller kidneys, as determined by ultrasound [46], and infants with intrauterine growth retardation have high blood angiotensin II levels. Chronic (3-day) infusion of angiotensin to the ovine fetus at mid-gestation causes a diuresis and an increase in blood pressure and causes a decrease in kidney renin gene expression (K.M. Moritz and E.M. Wintour, unpublished observations). It does not, however, affect expression of the angiotensin receptors. Later in gestation (120 days of gestation), a 3-day infusion of angiotensin results in the complete abolition of renin gene expression and causes expression of the AT1 receptor to decrease by about 50%. This indicates the kidney is sensitive to changes in the RAS from at least mid-gestation. Increased levels of angiotensin II may also have other effects, including causing an increase in levels of AQP 1 and 2 gene expression in the kidney [33]. In addition, angiotensin II has been proposed as a renal growth factor [47] for both mesangial and tubular cells. These effects are mediated by the AT1 receptor and may involve oncogene activation and collagen synthesis [48].

Concluding remarks

There is increasing interest in the role of the mesonephros as an important organ during fetal development, not merely as a source for the formation of the metanephros. The metanephros also has a number of functions, but whilst in utero its major role is to ensure the production of large volumes of urine for adequate fetal fluids. Hormonal systems (AVP, angiotensin II) are also modified during development to allow the metanephros to function in this manner.

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LITERATURE ABSTRACTS

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Isolation and characterization of verocytotoxin-producing *Escherichia coli* O157 strains from Dutch cattle and sheep

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In the periods from July to November 1995 and 1996, fecal samples from Dutch cattle and sheep were collected at the main slaughterhouses of The Netherlands, located at diffeent geographic sites. The samples were examined for the presence of verocytotoxin (VT)-producing *Escherichia coli* (VTEC) of serogroup 0157. E. coli O157 strains could be isolated from 57 (10.6%) of 540 adult cattle, 2 (0.5%) of 397 veal calves, 2 (3.8%) of 52 ewes, and 2 (4.1%) of 49 lambs. Immunomagnetic separation with O157-specific-antibody-coated beads appeared to be significantly more sensitive than conventional plating for detection of the organism in feces. With the exception of two isolates from adult cattle which appeared to be negative for VT genes, all animal isolates were positive for both VT (VT1 and/or VT2) and E. coli attaching-and-effacing gene sequences, and therefore, they were regarded as potential human pathogens. Although genomic typing by pulsed-field gel electrophoresis revealed a wide variety of distinct restriction patterns, comparison of the 63 animal isolates with 33 fecal O157 VTEC strains previously isolated from humans with the diarrhea-associated form of the hemolytic-uremic syndrome by their phage types and VT genotypes showed a marked similarity between animal and human isolates: 30 (90.9%) of the 33 human isolates appeared to be of E. coli O157 strain types also isolated from cattle and sheep. It was concluded that Dutch cattle and sheep are an important reservoir of E. coli O 157 strains that are potentially pathogenic for humans.

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Nephromegaly in infancy and early childhood: a risk factor for Wilms tumor in Beckwith-Wiedemann syndrome

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Objective Beckwith-Wiedemann Syndrome (BWS) is an overgrowth syndrome associated with macrosomia, omphalocele, macroglossia, visceromegaly and Wilms tumor (WT). We conducted a case-control study in children with BWS to examine whether nephromegaly increases the risk of WT.
Methods The BWS Registry was used to identify control and case patients. Control patients were defined as children with BWS who were older than 6 years and had no imaging evidence of renal disease or previous WT and for whom complete records were available; 31 patients met these criteria. Case patiens were defined as children with BWS who had WT and screening renal imaging before the diagnosis of WT; 12 of these patients had serial screening images before diagnosis of WT and comprised the study population. Only renal images obtained before the diagnosis of WT was made were used to assess renal length.
Results All 12 patients with WT had nephromegaly (> or =95th percentile of age adjusted renal length) on serial screening studies. Only four of 31 control patients (specificity=86%) had nephromegaly resulting in an odds ratio of 72 (95% confidence interval=13–391) for the risk of WT with nephromegaly.
Conclusions In patients with BWS, persistent nephromegaly is a strong risk factor for the development of WT. If screening for WT is done in this population, infants with nephromegaly should be considered those at greatest risk for WT, and screening may be best targeted at this group.