Vasoactive Factors and Blood Pressure in Children

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INTRODUCTION

Vasoactive peptide systems play a critical role in the regulation of arterial blood pressure (BP). Inappropriate stimulation or deregulation of cross talk between diverse vasomotor factors contributes in a major way to the development of hypertension, cardiovascular disease, and renal disease in children. Understanding how derangements in vasoactive factor systems may lead to these health problems might potentially prevent disease from occurring. This chapter will review new advances in physiology, biochemistry, pathophysiology,
and function of the renal and systemic vasoactive systems with special emphasis on their role in the pathogenesis of hypertension in children.

THE RENIN–ANGIOTENSIN SYSTEM

The renin–angiotensin system (RAS) plays a fundamental role in the regulation of arterial BP. Emerging evidence suggests that many tissues have a local tissue-specific RAS, which is of major importance in the regulation of the angiotensin (Ang) levels within many organs (1, 2). The RAS includes multiple components. The enzyme renin cleaves the substrate, angiotensinogen (AGT), to generate Ang I [Ang-(1–10)] (Fig. 1). Ang I is converted to Ang II [Ang-(1–8)] by angiotensin-converting enzyme (ACE). ACE expression on endothelial cells of many vascular beds including those in the kidney, heart, and lung allows systemic formation of Ang II, the most powerful effector peptide hormone of the RAS, throughout the circulation (3–5). Most of hypertensinogenic actions of Ang II are attributed to the AT$_1$ receptor (AT$_1$R) (6). Additionally, there are further pathways by which angiotensins may be formed—Ang II via chymase in tissues and Ang II metabolites via ACE2, as well as via endopeptidases.

![Fig. 1. Renin-Angiotensin System, with focus on target effects of Angiotensin II and alternate pathways of Angiotensin metabolism.](image)

ANGIOTENSINOGEN

Angiotensinogen (AGT) is formed and constitutively secreted into the circulation by the hepatocytes (7). In addition, AGT mRNA and protein are expressed in kidney proximal tubules, central nervous system, heart, adrenal gland, and other tissues (8,9). Although AGT is the only substrate for renin, other enzymes can cleave AGT to form Ang I or Ang II (Fig. 1) (10,11). Expression of the AGT gene is induced by Ang II, glucocorticoids, estrogens, thyroxine, and sodium depletion (9,12,13).
A number of AGT polymorphisms appear to influence BP level. For example, an A/G polymorphism at −217 in the promoter of the AGT gene may play an important role in hypertension in African-Americans (14).

PRORENIN, RENIN, AND (PRO)RENIN RECEPTOR

The major site of renin synthesis is in the juxtaglomerular cells of the afferent arterioles of the kidney, first as preprorenin (15). The human renin gene, which encodes preprorenin, is located on chromosome 1 (16). Cleavage of a 23-amino acid signal peptide at carboxyl terminus of preprorenin generates prorenin. Prorenin is then converted to active renin by cleavage of 43-amino acid N-terminal prosegment by proteases (5,17). The kidney secretes both renin and prorenin into the peripheral circulation. Plasma levels of prorenin are approximately tenfold higher than those of renin (18). Renin release is controlled relatively rapidly by baroreceptors in the afferent arterioles, chloride-sensitive receptors in the macula densa (MD) and juxtaglomerular apparatus, and renal sympathetic nerve activity in response to changes in posture or effective circulating fluid volume (Fig. 2) (19–22). Inhibition of renin secretion in response to an increase in NaCl at the MD is adenosine dependent, whereas stimulation of renin release by a low perfusion pressure depends on cyclooxygenase-2 and neuronal nitric oxide (NO) synthase (NOS) (23–25). In contrast, changes in AGT synthesis occur relatively slowly and thus are less responsible for the dynamic regulation of plasma Ang I and Ang II than changes in renin (3,26). In addition, the circulating concentrations of AGT are more than 1000 times greater than the plasma Ang I and Ang II levels (1). Therefore, renin activity is the rate-limiting factor in Ang I formation from AGT (5). Although Ang II can be generated from AGT or Ang I via renin/ACE-independent pathways (10,11), the circulating levels of Ang II reflect primarily the consequences of the action of renin on AGT (27).

Recently, the renin/prorenin–(pro)renin receptor complex has emerged as a newly recognized pathway for tissue Ang II generation. In addition to proteolytic activation, prorenin may be activated by binding to (pro)renin receptor (28).

The (pro)renin receptor is expressed on mesangial and vascular smooth muscle cells and binds both prorenin and renin (29). Binding of renin or prorenin to (pro)renin receptor induces a conformational change of prorenin, facilitating catalytic activity and the conversion of AGT to Ang I (28). A direct pathological role of the (pro)renin receptor in hypertension is suggested by the findings of elevated blood pressure in rats with transgenic overexpression of the human (pro)renin receptor (30).

**Fig. 2.** Feedback loop between renin secretion and end-effects of the renin-nagiotensin-aldosterone system.
ANGIOTENSIN-CONVERTING ENZYME

Angiotensin-converting enzyme (ACE) is involved in the posttranslational processing of many polypeptides, the most notable of which are Ang I and bradykinin (BK) (Figs. 1 and 3). There are two ACE isozymes, somatic and testicular, transcribed from a single gene by differential utilization of two distinct promoters (31). Human somatic ACE contains 1,306 amino acids and has a molecular weight of 140–160 kilodaltons (kDa). In the kidney, ACE is present as an ectoenzyme in glomerular vascular endothelial and proximal tubular cells (32). ACE localized in glomerular endothelium may regulate intraglomerular blood flow, whereas ACE expressed in the proximal tubular epithelia and postglomerular vascular endothelium may play an important role in the regulation of tubular function and postglomerular circulation. Polymorphisms in the ACE gene appear to be important in blood pressure regulation. In particular, an insertion/deletion (I/D) polymorphism of 287 base pairs in exon 16 is associated with hypertension (33). Persons with the D allele have higher plasma ACE levels and higher rates of hypertension.

![Fig. 3. Bradykinin-kinase system with focus on end-effects of bradykinin and its degradation products.](image)

ANGIOTENSIN II RECEPTORS

Ang II acts via two major types of G-protein-coupled receptors (GPCRs): AT\(_1\)R and AT\(_2\)R. In rodents, AT\(_1\)R has two distinct subtypes, AT\(_{1A}\) and AT\(_{1B}\), with greater than 95% amino acid sequence homology (34). In the kidney, AT\(_1\)R mRNA has been localized to proximal tubules, the thick ascending limb of the loop of Henle, glomeruli, arterial vasculature, vasa recta, arcuate arteries, and juxtaglomerular cells (35). Activation of Ang II binding to the AT\(_1\)R increases BP by (1) direct vasoconstriction and increase in peripheral vascular resistance; (2) stimulation of Na reabsorption via the sodium hydrogen exchanger 3 (NHE3) at the proximal nephron and by NHE3 and bumetanide-sensitive cotransporter 1 (BSC-1) at the medullary thick ascending limb of the loop of Henle, and (3) stimulation of aldosterone biosynthesis and secretion by the adrenal zona glomerulosa (Fig. 2) (36–38). AT\(_1\)R activation also stimulates vasopressin and endothelin secretion and stimulates the sympathetic nervous system, and the proliferation of vascular smooth muscle and
mesangial cells \((39-41)\). The \(\text{AT}_2\)R has 34% homology with \(\text{AT}_{1A}\) or \(\text{AT}_{1B}\) receptors \((42)\). The \(\text{AT}_2\)R is expressed in the glomerular epithelial cells, proximal tubules, collecting ducts, and parts of the renal vasculature of the adult rat \((43)\). In contrast to the \(\text{AT}_1\)R, the \(\text{AT}_2\)R elicits vasodilation by increasing the production of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) either by stimulating formation of bradykinin or by direct activation of NO production \((44-46)\). In addition, the \(\text{AT}_2\)R promotes renal sodium excretion and inhibits proliferation in mesangial cells \((44,47,48)\). Thus, the \(\text{AT}_2\)R generally appears to oppose \(\text{AT}_1\)R-mediated effects on blood pressure, cardiovascular and renal growth, fibrosis, and remodeling, as well as RBF, fibrosis, and sodium excretion.

**ANGIOTENSIN-CONVERTING ENZYME 2**

ACE2 is a homologue of ACE that is abundantly expressed in the kidney and acts to counterbalance ACE activity by promoting Ang II degradation to the vasodilator peptide Ang-(1–7) \((49,50)\). Ang-(1–7) acts via the GPCR Mas encoded by the \(\text{Mas}\) protooncogene and counteracts Ang II–AT1R-mediated effects \((51,52)\). An important role for ACE2 in the regulation of BP is suggested by the findings of a decreased ACE2 expression in the kidney of hypertensive rats and reduction of BP following genetic overexpression of ACE2 in their vasculature \((53,54)\). Although ACE2-null mice are normotensive and have normal cardiac structure and function, they exhibit enhanced susceptibility to Ang II-induced hypertension \((55)\). Moreover, Mas-deficient mice exhibit increased blood pressure, endothelial dysfunction, and an imbalance between NO and reactive oxygen species \((56)\). Other major degradation products of Ang II include Ang III \([\text{Ang-}(2-8)]\) and Ang IV \([\text{Ang-}(3-8)]\). These peptides have biological activity, but their plasma levels are much lower than those of Ang II or Ang-(1–7) \((57)\).

**DEVELOPMENTAL ASPECTS OF THE RAS**

The developing metanephric kidney expresses all the components of the RAS (Table 1). The activity of the renal RAS is high during fetal and neonatal life and declines during postnatal maturation \((58,59)\). Immunoreactive Ang II levels are higher in the fetal and newborn than in adult rat kidney \((59)\). The ontogeny of \(\text{AT}_1\)R and \(\text{AT}_2\)R mRNA in the kidney differs—\(\text{AT}_2\)R is expressed earlier than \(\text{AT}_1\)R, peaks during fetal metanephrogenesis, and rapidly declines postnatally \((60,61)\). \(\text{AT}_1\)R mRNA expression increases during gestation, peaks perinatally, and declines gradually thereafter \((60-62)\). ACE mRNA and enzymatic activity are expressed in the developing rat kidney, where they are subject to regulation by endogenous Ang II and bradykinin \((59,62)\). In addition, the developing kidney expresses considerable ACE-independent Ang II-generating activity \((63)\), which may compensate for the low ACE levels in the early metanephros \((59)\). The role of the ACE2–Ang-(1–7)–Mas axis and the (pro)renin receptor in developmental origins of hypertension remains to be determined. Functionally, Ang II, acting via the \(\text{AT}_1\)R, counteracts the vasodilator actions of bradykinin on the renal microvasculature of the developing rat kidney \((64)\). Premature infants exhibit markedly elevated PRA levels, a finding that is inversely related to postconceptual age \((65)\). In healthy children, plasma renin activity (PRA) is high during the newborn period and declines gradually toward adulthood \((66)\).

Pharmacologic or genetic interruption of the RAS during development alters BP phenotype and causes a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT) in rodents and renal tubular dysgenesis (RTD) in humans (Table 2) \((67,68)\).
Table 1

<table>
<thead>
<tr>
<th>Component</th>
<th>E12</th>
<th>E14</th>
<th>E15</th>
<th>E16</th>
<th>E19</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGT</td>
<td>Mouse: UB, SM</td>
<td>UB, SM, PT</td>
<td>Rat: UB, SM</td>
<td>UB, SM, PT</td>
<td>PT</td>
<td>(155)</td>
</tr>
<tr>
<td>Renin</td>
<td>Mouse: precursor cells present M of entire kidney M, close to V and G V, G</td>
<td></td>
<td>Rat: V</td>
<td>V</td>
<td>V</td>
<td>(157)</td>
</tr>
<tr>
<td>ACE</td>
<td>Rat: PT, G, CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(158)</td>
</tr>
<tr>
<td>AT₁</td>
<td>Mouse: UB, M</td>
<td>UB, G</td>
<td>UB, V</td>
<td>PT, UB, SM, G</td>
<td>PT, DT</td>
<td>(155)</td>
</tr>
<tr>
<td>AT₂</td>
<td>Mouse: MM</td>
<td>MM SM</td>
<td>Medullary SM, under renal capsule</td>
<td></td>
<td></td>
<td>(62)</td>
</tr>
</tbody>
</table>

AGT, angiotensinogen; ACE, angiotensin-converting enzyme; AT₁/AT₂, angiotensin II receptors; UB, ureteric bud; M, mesenchyme; SM, stromal mesenchyme; PT, proximal tubule; G, glomeruli; V, renal vessels; CD, collecting duct.

Adapted from (159), with permission from Springer.
Table 2
Renal and Blood Pressure Phenotypic Effects of Genetic Inactivation of the Renin–Angiotensin System Genes in Mice

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function of gene</th>
<th>Renal phenotype</th>
<th>Blood pressure</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGT</td>
<td>Renin substrate</td>
<td>Vascular thickening</td>
<td>Very low</td>
<td>(160)</td>
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<tr>
<td></td>
<td></td>
<td>Interstitial fibrosis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Delayed glomerular maturation</td>
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<td></td>
<td></td>
<td>Hypoplastic papilla</td>
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<td></td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reduced ability to concentrate urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin</td>
<td>Enzyme that generates ANG I from AGT</td>
<td>Arterial wall thickening</td>
<td>Very low</td>
<td>(163)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial fibrosis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Glomerulosclerosis</td>
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<td></td>
<td></td>
<td>Hypoplastic papilla</td>
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<td></td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>Enzyme which generates ANG II from ANG I</td>
<td>Arterial wall thickening</td>
<td>Very low</td>
<td>(164)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic papilla and medulla</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reduced ability to concentrate urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT1A/B</td>
<td>Ang II receptor</td>
<td>Decreased kidney weight</td>
<td>Very low</td>
<td>(165)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed glomerular maturation</td>
<td></td>
<td>(166)</td>
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<tr>
<td></td>
<td></td>
<td>Arterial wall thickening</td>
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<td></td>
<td></td>
<td>Interstitial fibrosis</td>
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<td></td>
<td>Tubular atrophy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hypoplastic papilla and medulla</td>
<td></td>
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<td></td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reduced ability to concentrate urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT1A</td>
<td>Ang II receptor</td>
<td>Normal or mild papillary hypoplasia</td>
<td>Moderately low</td>
<td>(6)</td>
</tr>
<tr>
<td>AT1B</td>
<td>Ang II receptor</td>
<td>Normal</td>
<td>Normal</td>
<td>(167)</td>
</tr>
<tr>
<td>AT2</td>
<td>Ang II receptor</td>
<td>Duplicated ureters</td>
<td>High</td>
<td>(168)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
<td>(169)</td>
</tr>
</tbody>
</table>

Therefore, RAS inhibitors should not be used during pregnancy and should not be used postnatally until nephrogenesis is completed. Beyond these periods of life, high activity of the RAS coupled with persistent expression of the renal AT1R provide the foundation for the use of the classical RAS inhibitors (ACE inhibitors and AT1R antagonists) in the
treatment of children with RAS-dependent hypertension (e.g., renovascular hypertension). In addition, both ACE inhibitors and angiotensin receptor blockers may be beneficial in children with primary hypertension, particularly in obese adolescents, who exhibit elevated plasma renin activity (69). Recent availability of aliskiren, the first direct inhibitor of (pro)renin receptor, offers new possibilities in antihypertensive therapy in children that remain to be explored.

**ALDOSTERONE**

Ang II, acting via the AT$_1$R, stimulates an increase in transcription and expression of the rate-limiting enzyme in the biosynthesis of aldosterone, CYP 11B2 (aldosterone synthase) in the zona glomerulosa of the adrenal glands (36). Aldosterone stimulates reabsorption of Na$^+$ and secretion of potassium by principal cells in the collecting duct. In turn, the retained Na$^+$ is responsible for increased extracellular fluid volume that increases BP. Secretion of aldosterone is stimulated by high plasma potassium concentration and adrenocorticotropic hormone (ACTH), and inhibited by atrial natriuretic peptide (ANP) (70–72). Aldosterone-dependent Na$^+$ reabsorption is due to upregulation of epithelial Na$^+$ channel-$\alpha$ (alfa) (ENaC$\alpha$) subunit gene expression and increased apical density of ENaC channels due to serum- and glucocorticoid-induced kinase-1 (Sgk1)-induced disinhibition of Nedd4-2-triggered internalization and degradation of ENaC (73). Aldosterone downregulates the expression of histone H3 methyltransferase Dot1a and the DNA-binding protein Af9 complexed with chromatin within the ENaC$\alpha$ (alfa) 5' flanking region (74). In addition, aldosterone-induced Sgk1 phosphorylates Ser435 of Af9, causing disruption of the protein–protein interactions of Dot1a, a histone H3 lysine 79 (H3K79) methyltransferase, and Af9. This results in hypomethylation of histone H3 Lys79 and release of transcriptional repression of the ENaC$\alpha$ (alfa) gene. The important role of aldosterone in childhood hypertension is underscored by the ability of mineralocorticoid receptor antagonists not only to reduce elevated BP due to hyperaldosteronism (e.g., adrenal hyperplasia) effectively, but also to offer survival benefits in heart failure and augment potential for renal protection in proteinuric chronic kidney disease.

**GLUCOCORTICOIDS**

Glucocorticoids are vital for normal development and control of hemodynamic homeostasis. Cortisol or dexamethasone infusion increases BP in the fetal sheep (75,76). Dexamethasone increases BP in Sgk1$^{+/+}$ but not in Sgk1$^{-/-}$ mice (77), indicating that hypertensinogenic effects of glucocorticoids on BP are mediated in part via Sgk1. A higher ratio of cortisol to cortisone in venous cord blood is associated with higher systolic blood pressure later in life in humans (78), suggesting that increased fetal glucocorticoid exposure may account for higher systolic blood pressure in childhood. However, no differences in BP and cardiovascular function are detected at school age in children treated neonatally with glucocorticoids for chronic lung disease (79). It is possible that the functional consequences of glucocorticoid therapy during neonatal life may manifest only later in life. However, deleterious effects of excess glucocorticoids on childhood BP are apparent, for example, in conditions such as Cushing’s syndrome or glucocorticoid-remediable aldosteronism.
KALLIKREIN–KININ SYSTEM

The kallikrein–kinin system (KKS) plays an important role in the regulation of blood pressure. Kinins, including bradykinin (BK), are formed from kininogen by kininogenase tissue kallikrein (80) (Fig. 3). Bradykinin is degraded by ACE, which is also called kininase II (81). Kinins act by binding to the bradykinin receptors B1 (B₁R) and B₂ (B₂R). The B₁R is activated by Des-Arg⁹-BK produced from BK by kininase I, which mediates tissue injury and inflammation (82). The renal and cardiovascular effects of BK are mediated predominantly through the B₂R. During development kininogen is expressed in the ureteric bud and stromal interstitial cells of the E15 metanephros in the rat and, presumably, in other mammals (83). Following completion of nephrogenesis, kininogen is localized in the collecting duct. The main kininogenase, true tissue kallikrein, is encoded by the KLK1 gene (84). Transcription of KLK1 gene is regulated by salt and protein intake, insulin, and mineralocorticoids. Expression of the KLK1 gene within the kidney is suppressed in chronic phase of renovascular hypertension (83).

In the developing rat kidney, kallikrein mRNA and immunoreactivity are present in the connecting tubule (85). In the mature kidney, tissue kallikrein mRNA is expressed in the distal tubule and glomeruli (86). Thus, BK can be generated intraluminally from kininogen present in the collecting duct or in the interstitium. BK generated intraluminally causes natriuresis, whereas interstitial BK may regulate medullary blood flow (87). The proximity of the distal tubule to the afferent arteriole may allow kallikrein or BK to diffuse from the distal tubular cells and act in a paracrine manner on the preglomerular microvessels (88). The human B₁R and B₂R genes are located on chromosome 14 and demonstrate 36% genomic sequence homology (89). Both B₁R and B₂R are members of the seven-transmembrane GPCR family. During metanephrogenesis, B₂R is expressed in both luminal and basolateral aspects of collecting ducts, suggesting that activation of B₂R is important for tubular growth and acquisition of function (90). The expression of B₁R is inducible rather than constitutive. In contrast to B₂R, B₁R is not expressed in significant levels in normal tissues (82). Although BK does not appear to be a primary mediator of the maturational rise in RBF in the rat, its vasodilatory effects in the developing kidney are tonically antagonized by Ang II AT₁R (65). Stimulation of the B₂R during adult life stimulates production of nitric oxide and prostaglandins resulting in vasodilation and natriuresis (91). The importance of the KKS in the regulation of BP is underscored by the finding of elevated BP in mice that lack the B₂R (92). Moreover, B₂R-null mice are prone to early onset of salt-sensitive hypertension (93). Interestingly, B₁R receptor blockade in B₂R-null mice produces a significant hypertensive response (94), indicating that both receptors participate in the development of hypertension. In keeping with this hypothesis, single-nucleotide polymorphisms in the promoters of both B₁R and B₂R genes are associated with hypertension in African-Americans, indicating that the two receptors play a role in BP homeostasis in humans (95). The direct potential role of the KKS in childhood hypertension is further highlighted by studies showing that endogenous bradykinin contributes to the beneficial effects of ACE inhibition on BP in humans (96).

ARGININE VASOPRESSIN

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the hypothalamus and released in response to increased plasma osmolality, decreased arterial pressure, and reductions in circulating blood volume. Three subtypes of vasopressin
receptors, V₁R, V₂R, and V₃R, mediate vasoconstriction, water reabsorption, and central nervous system effects, respectively. In addition, stimulation of the V₂R induces endothelial NOS expression and promotes NO production in the renal medulla, which attenuates the V₁R-mediated vasoconstrictor effects (97). In adult species, AVP supports arterial BP when both the sympathetic system and the RAS are impaired by sympathetic blockade (98). Treatment with a V₁R antagonist has no effect on arterial BP in fetal sheep (99,100). In contrast, antagonism of V₁R during hypotensive hemorrhage impairs the ability of the fetus to maintain BP (101). Thus, endogenous AVP has little impact on basal hemodynamic homeostasis of the fetus, but plays an important role in vasopressor response to acute stress such as hemorrhage.

ENDOTHELIUM-DERIVED VASOACTIVE FACTORS

Nitric Oxide

Hypertension is associated with abnormal endothelial function in the peripheral, coronary, and renal vasculatures. Nitric oxide (NO) is an important mediator of endothelium-dependent vasodilation. NO enhances arterial compliance, reduces peripheral vascular resistance, and inhibits proliferation of vascular smooth muscle cells (102). The major source of NO production in the rat kidney is the renal medulla where NO regulates medullary blood flow, natriuresis, and diuresis (103,104). NO promotes pressure natriuresis via cGMP (105). The effects of Ang II or AVP on medullary blood flow are buffered by the increased production of NO (103), indicating that endogenous NO tonically counteracts the effects of vasoconstrictors within the renal medullary circulation. Interestingly, endothelial dysfunction is not only a consequence of hypertension, but may predispose to the development of hypertension. In this regard, impaired endothelium-dependent vasodilation has been observed in normotensive children of patients with essential hypertension compared with those without a family history of hypertension (106), demonstrating that an impairment in NO production precedes the onset of essential hypertension. Acute antagonism of NO generation leads to an increase in BP and decreases RBF in the fetal sheep (107). In fetal rat kidneys, endothelial NO synthase (eNOS) immunoreactivity is first detected in the endothelial cells of the intrarenal capillaries on E14 (108). These findings suggest that eNOS may play a role in regulating renal hemodynamics during fetal life. Moreover, eNOS-knockout mice exhibit abnormal aortic valves, congenital atrial defects, and ventricular septal defects, indicating that eNOS-derived NO plays an important role in the development of the circulatory system (109). The effect of intrarenal infusion of NO antagonist L-NAME on decreases in RBF and GFR is more pronounced in the newborn than adult kidney (110). These effects of NO may act to oppose high RAS activity present in the developing kidney.

Asymmetrical Dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of eNOS (111). Infusion of ADMA increases BP and renal vascular resistance, and decreases renal plasma flow during adulthood (112). ADMA levels in fetal umbilical venous plasma are higher than in maternal plasma (113). However, low resistance to umbilical blood flow is maintained despite substantially higher fetal ADMA levels. It is therefore conceivable that NO is a key modulator of fetal vascular tone. Hypertensive children have higher plasma ADMA levels compared with normotensive subjects (114). In contrast, plasma ADMA levels do not differ between normotensive and hypertensive young adults (115). Moreover, plasma ADMA
correlate negatively with vascular resistance (115), suggesting that in a physiological setting ADMA levels in subjects with elevated vascular tone may be lowered to compensate for inappropriately high resistance.

**Endothelins**

Endothelins (ETs) are vasoconstrictor peptides produced by endothelial cells (116,117). Three ETs were described: endothelin-1 (ET-1), -2 (ET-2), and -3 (ET-3). The hemodynamic effects of ET-1 are mediated by ET\(_A\) and ET\(_B\) GPCRs. In the kidney, ET-1 mRNA is expressed in the glomeruli and medullary collecting ducts (118,119). ET receptors are located in podocytes, glomeruli, afferent and efferent arterioles, proximal tubules, medullary thick ascending limbs, and collecting ducts (120). The ET\(_B\) receptor activation causes natriuresis and vasodilation via release of NO and PGE\(_2\), whereas renal vasoconstriction is mediated by the ET\(_A\) receptor (121). In the fetal lamb, the ET\(_A\) and ET\(_B\) receptors expressed on vascular smooth muscle cells mediate vasoconstriction, whereas ET\(_B\) receptors located on endothelial cells mediate vasodilation (122,123). In the renal circulation of fetal sheep, ET-1, acting via the ET\(_B\) receptor, causes vasodilation (124). However, ET\(_A\) receptor-mediated vasoconstriction also contributes to the regulation of the fetal renal vascular tone (125). The critical role for the renal ET-1 and ET\(_A\)/ET\(_B\) receptors in the regulation of systemic BP is demonstrated by the finding of increased BP in mice with collecting duct-specific genetic inactivation of either ET-1 or both ET\(_A\) and ET\(_B\) receptors (126,127). Moreover, BP increases further with high salt intake, indicating that combined ET\(_A\)/ET\(_B\) receptor deficiency causes salt-sensitive hypertension.

**NATRIURETIC PEPTIDES**

Natriuretic peptides include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), urodilatin, and Dendroaspis-type natriuretic peptide (DNP) (128–131). Natriuretic peptides act by binding to three guanylyl cyclase-linked receptors: NPR-A, NPR-B, and NPR-C (132). In the adult heart, ANP and BNP are stored in atrial and ventricular myocytes, respectively, released in response to atrial stretch, increased BP, atrial tachycardia, or increased osmolality (132,133), and are rapidly degraded in the lung and kidney by neutral endopeptidase (134). ANP and BNP reduce secretion of renin and aldosterone, and antagonize the effects of Ang II on vascular tone and renal tubular reabsorption to cause natriuresis, diuresis, a decrease in BP, and intravascular fluid volume (135). ANP and BNP peptide levels are higher in fetal than adult ventricles, indicating that the relative contribution of ventricular ANP is greater during embryonic than adult life (136–138). ANP and BNP mRNAs are expressed on E8 in the mouse and increase during gestation, suggesting that both ANP and BNP play a role in the formation of the developing heart. Circulating ANP levels are higher in the fetal than adult rat or sheep (137,139). Infusion of ANP into the circulation of fetal sheep decreases BP and causes diuresis (140). ANP secretion during postnatal development is stimulated in response to similar physiological stimuli as in the adult animal and can be induced by Ang II, volume loading, hypoxia, or increase in osmolality (139,141). Plasma levels of ANP are higher in preterm than term infants (142). In the full-term infants, circulating ANP levels increase during the first week of life and decrease thereafter (143). The initial postnatal increase in ANP may mediate diuresis during the transition to extrauterine life. Subsequent decrease in plasma ANP may serve to conserve sodium required for rapid growth. Although BP remains normal
in BNP-null mice (144), ANP-null mice develop hypertension later in life (145). Mice lacking NPR-A receptor exhibit cardiac hypertrophy and have elevated BP, indicating that the ANP and BNP play an important role in the regulation of myocyte growth and BP homeostasis during development (146,147).

**VASOACTIVE FACTORS AND DEVELOPMENTAL PROGRAMMING OF HYPERTENSION**

An inverse relationship between birth weight or maternal undernutrition and adult BP led to the concept of developmental programming of hypertension (147). Brain RAS is activated by low protein (LP) diet and hypertensive adult offspring of LP-fed dams have increased pressor response to Ang II (148,149). Thus, inappropriate activation of the RAS may link fetal life to childhood and adult hypertension. Interestingly, LP maternal diet has been reported to result in decreased methylation of the promoter region of AT1B in the offspring (150). It is conceivable that epigenetic modifications of the AT1B gene may represent one of the mechanisms implicated in developmental programming of hypertension by an aberrant RAS. LP diet or caloric restriction during gestation causes a decrease in the renal kallikrein activity, blunted vasorelaxation to NO infusion, an increase in vascular superoxide anion concentration, and a decrease in superoxide dismutase activity in offspring of dams with such restricted diets (151–153). In addition, heterozygous eNOS offspring born to eNOS-null mothers exhibit impaired endothelium-dependent vasodilation compared to heterozygous pups born to eNOS+/+ mothers (154). These observations indicate that impairment in endothelium-dependent vascular function is associated with developmentally programmed hypertension and that the eNOS maternal genotype modulates a genetic predisposition to hypertension. Further studies are needed to establish the mechanisms by which alterations in the antenatal environment impact vasoactive factor systems and their interplay to program hypertension during postnatal life.

**SUMMARY**

Many vasoactive substances regulate cardiovascular homeostasis during development, and more are discovered each year. Many cardiovascular factors exert pleiotropic actions both systemically and within diverse organ systems. Continued discovery of new vasoactive substances and more complete knowledge of their role during development will increase our understanding of the developmental origin of hypertension and cardiovascular disease and should help in the development of strategies that will minimize the impact of these substances on hypertension. Further work is needed to define more precisely the role of emerging cardiovascular regulatory factors and to understand their growing relevance to a number of conditions in animal models of human disease and in human diseases including hypertension.

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Pediatric Hypertension
(Eds.) J.T. Flynn; J.R. Ingelfinger; R.J. Portman
2011, VIII, 692 p. 64 illus., 9 in color., Hardcover
A Humana Press product