Age-dependent renal responses to the bradykinin B₂-receptor antagonist icatibant in conscious lambs

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Patel, Avni, and Francine G. Smith. Age-dependent renal responses to the bradykinin B₂-receptor antagonist icatibant in conscious lambs. Am J Physiol Regulatory Integrative Comp Physiol 281: R1311–R1318, 2001.—To investigate the role of endogenously produced bradykinin in modulating renal function during postnatal maturation, various parameters of glomerular and tubular function were measured for 1 h before and after intravenous injection of 12.5 μg/kg of the specific B₂-receptor antagonist icatibant to conscious, chronically instrumented lambs aged ~1 (n = 7) and ~6 wk (n = 7). In response to icatibant, and in the absence of any changes in renal hemodynamics, there was an ~80% decrease in glomerular filtration rate (GFR) at 20 min in 1-wk-old lambs that was sustained for 60 min; in 6-wk-old lambs, there was an ~70% decrease in GFR by 20 min, with control levels being reached by 40 min. Icatibant administration was also associated with significant decreases in urinary flow, Cl⁻, and K⁺ excretion rates that were similar in both groups of lambs, whereas Na⁺ excretion decreased only in 6-wk-old lambs. We conclude that bradykinin modulates glomerular and tubular function in an age-dependent manner.

kinins; glomerular filtration rate; Na⁺ excretion; renin; kallikrein-kinin system

THE KALLIKREIN-KININ SYSTEM plays an important role in a number of physiological processes, including pain, inflammation, vascular permeability, and smooth muscle contractility. Two types of cell surface receptors mediate these varied physiological effects of kinins and are designated as B₁ and B₂. Most of the physiological responses to bradykinin appear to be mediated through activation of the B₂ receptor, which is the most prevalent receptor subtype within the body. In the kidney, B₂ receptors have been localized to cortical epithelium, medullary interstitium, and glomeruli and mesangial cells (13) and bradykinin, which activates B₂ receptors, is known to regulate renal hemodynamics as well as glomerular ultrafiltration and tubular function.

Previous studies in newborns of relatively altricial species, including rats and mice, provided evidence that various components of the renal kallikrein-kinin system are developmentally regulated (2, 4, 8, 19). For example, bradykinin synthesis and B₂-receptor gene expression are activated in the developing rat kidney (7, 8). There is an increase in mRNA expression of glomerular B₂ receptors over the first weeks of postnatal life in the rat kidney along with increased bradykinin binding capacity and a rise in bradykinin-induced release of PGE₂ from isolated glomeruli (2). There is also an increase in renal cortical kallikrein activity as maturation proceeds in the rat, consistent with an enhancement of kinin production and subsequently B₂-receptor activation (2). Studies by El-Dahr and Chao (6) also showed that the transition from newborn to adult life in rats is associated with six- and fourfold increases in renal kallikrein content and its mRNA and that B₂ mRNA levels are 30- to 40-fold higher in newborn than adult kidneys (31). In addition, pharmacological blockade of B₂ receptors for the first 2 wk of postnatal life in rats decreases body weight, kidney weight, and kidney DNA content (31). In recent experiments in transgenic mice by the same group (9), B₂-receptor mRNA was shown to be expressed on the apical membrane of the ureteric bud branches during fetal life and on both apical and basolateral membranes of collecting ducts later in life. Furthermore, it was shown that mice deficient in the B₂-receptor gene and salt loaded during embryogenesis acquired an aberrant kidney phenotype incompatible with postnatal survival (9). It has not been possible to further evaluate the physiological effects of bradykinin during fetal and newborn life in the mouse or rat due to the limits imposed by size and immaturity. In sheep, which is a relatively precocial species, the rate of kinin formation also appears to be developmentally regulated. It has not been possible to further evaluate the physiological effects of bradykinin during fetal and newborn life in the mouse or rat due to the limits imposed by size and immaturity. In sheep, which is a relatively precocial species, the rate of kinin formation also appears to be developmentally regulated. To date, there have been no studies into the ontogeny of B₂ receptors in sheep.

In recent experiments in conscious, chronically instrumented lambs (16), we investigated some of the physiological effects of kinins on systemic and renal hemodynamics. First, we measured the renal blood flow response to intra-arterial injection of the B₂-recept-
tor agonist bradykinin over the range of doses 0–800 ng/kg. Effects of bradykinin were age and dose dependent, the increase in renal blood flow being greater in 6- compared with 1-wk-old lambs. The ED_{50} renal blood flow response to bradykinin was 50 ng/kg in both age groups of lambs. Second, we measured the effects of intravenous administration of 12.5 μg/kg of the specific B_{2}-receptor antagonist d-Arg[His^{2}, Pro^{3}]bradykinin (icatibant). This dose attenuated the renal blood flow response to 50 ng/kg of bradykinin in both age groups of lambs for 60 min (16). Icatibant administration was associated with an age-dependent increase in mean arterial pressure, with little effect on heart rate or renal vascular resistance. We concluded from these studies in conscious lambs that B_{2} receptors as well as a functional signaling pathway are present on renal arterial endothelial cells soon after birth. However, it does not appear that endogenously produced bradykinin modulates renal hemodynamics during postnatal maturation.

In the present experiments, we set out to investigate the renal effects of endogenously produced kinins. To test the hypothesis that the effects of endogenous bradykinin on glomerular and tubular function are age dependent, we measured various parameters of renal function before and after administration of icatibant to two age groups of conscious, chronically instrumented lambs.

**METHODS**

Experiments were performed in conscious, chronically instrumented 1-wk-old lambs (n = 7), 7 ± 1 days of age and weighing 6.9 ± 0.8 kg, and 6-wk-old lambs (n = 7), 40 ± 3 days of age and weighing 11.6 ± 2.9 kg. Lambs were obtained from a local source (AndLyn Ranch, Alberta, Canada) and housed with their mothers in individual pens in the vivarium from a local source (AndLyn Ranch, Alberta, Canada) and housed with their mothers in individual pens in the vivarium, except during surgery and experiments. All surgical and experimental procedures were carried out in accordance with the “Guide to the Care and Use of Experimental Animals” provided by the Canadian Council on Animal Care and with the approval of the Animal Care Committee of the University of Calgary.

**Surgical procedures.** With the use of aseptic techniques, surgery was performed on newborn lambs 2–5 days after birth and on older lambs at least 3 days before the start of experiments, as previously described (16, 22, 23). Briefly, anesthesia was induced with a mask and halothane (3–4%) in oxygen, the trachea was intubated, and anesthesia was maintained by ventilating the lungs with halothane (0.5–1%) in a mixture of nitrous oxide and oxygen (3:1). Left and right femoral veins and arteries were catheterized (PE-160 catheter, Intramedic) for later intravenous infusions and arterial sampling; catheters were tunneled subcutaneously to exit the lamb on right and left flanks. By means of an abdominal midline incision, the bladder was then exposed, and a catheter was inserted directly across the bladder wall using a specially adapted feeding tube (Medi-Craft) for collection of urine and measurement of urinary flow rate during experiments. Through a right flank incision, the right renal artery was carefully dissected free of tissue, and an ultrasonic flow transducer was placed around the renal artery (3–4S, Transonics Instruments) for measurement of renal blood flow and calculation of renal plasma flow. On closure of incisions, all catheters and the flow transducer cable were secured in a body jacket (Lomir, Montreal) for safe storage between experiments. Antibiotics (5.0 mg/kg enrofloxacine, Baytril) were administered intramuscularly at surgery and at 12-h intervals thereafter for 48 h. Lambs were allowed to recover from surgery in a critical care unit for small animals (Shor-line, Schroer Manufacturing) with adjustable oxygen supply. All lambs were able to stand within 60 min of completion of surgery, at which time they were returned to the vivarium. Experiments were not begun until 3–5 days had elapsed after surgery; during this time, animals were trained to rest comfortably in a supportive sling in the laboratory environment.

**Experimental procedures.** On the day of an experiment, the animal was removed from the vivarium and placed in a supportive sling in the laboratory environment for at least 60 min. During this time, the bladder was allowed to drain. A priming dose of [1^{4}C]inulin (0.5 μCi/kg) in dextrose was injected intravenously followed by constant intravenous infusion of 0.25 μCi·h^{-1}·kg^{-1} for later measurement of glomerular filtration rate (GFR). An intravenous infusion of 5% dextrose in 0.9% sodium chloride was started at a rate of 4.17 ml·h^{-1}·kg^{-1} and continued for the duration of the experiment to assist in maintaining fluid balance.

Each experiment consisted of consecutive urinary collection periods for 1 h before (control, 3 × 20 min) and 1 h after (3 × 20 min) intravenous infusion over 10 min of 12.5 μg/kg of the specific bradykinin B_{2}-receptor antagonist icatibant. This dose was chosen in previous dose-response studies as that which attenuated the renal vasodilatory response to bradykinin for at least 60 min (16). At the end of each urinary collection period, urine volume was recorded and samples stored at -70°C for later determination of urinary electrolytes (Na^{+}, K^{+}, Cl^{-}) and urine osmolality. Arterial blood was also removed at the end of every urinary collection for immediate measurement of blood gas status and hematocrit; the remaining blood was centrifuged, and supernatant was removed and stored at -70°C for later determination of plasma electrolytes (Na^{+}, K^{+}, Cl^{-}) and plasma osmolality. Additional blood was removed during the second control collection and 20 and 60 min after icatibant for later measurement of plasma renin activity (PRA) and plasma levels of PGE. At the end of the experiment, the animal was administered a lethal dose of pentobarbital sodium and on postmortem, placement of catheters was verified, and the zero offset of the flow transducer was determined; right and left kidneys were removed and promptly weighed.

**Analytic procedures.** Urinary and plasma [1^{4}C]inulin levels were measured immediately after each experiment by liquid scintillation (Wallace 1410). Urine and plasma samples were later thawed to room temperature, and electrolytes (Na^{+}, K^{+}, Cl^{-}) and osmolalities were measured using a flame photometer (IL-943), chloride titrator (LabConco), and microhematocrit (Advanced Instruments model 3MO). A blood gas analyzer (Stat 3, NOVA Biomedical) was used to determine arterial pH, P_{O_{2}}, and P_{CO_{2}} immediately after blood withdrawal. A cooximeter (IL-292) was used to measure hemoglobin and oxyhemoglobin saturation. Hematocrit was determined in duplicate using a microhematocrit centrifuge (Clay Adams) and careful measurements using calipers and the methods of Brace (3). PRA and plasma levels of PGE were later determined on thawed plasma samples using standard radioimmunoassay procedures (12, 29).

**Computations.** GFR was calculated as the clearance of [1^{4}C]inulin. Fractional reabsorption (FR) of electrolytes (x) was determined from the ratio of electrolyte clearance (C_{x}) to GFR as follows: FR_{x}% = 1 − C_{x}/GFR × 100. Free water clearance (C_{H_{2}O}) was calculated as the difference between
urinary flow rate (V) and osmolar clearance. Filtration fraction (FF) was determined as GFR/RPF, where RPF is renal plasma flow.

Statistical analyses. Because values obtained during the three consecutive control urinary collections (3 × 20 min) were similar, these were averaged to one control value. Changes from control after icatibant were determined using multivariate ANOVA procedures for repeated measures. Where the F value was found to be significant, Newman-Keuls multiple comparison procedures were applied to determine where the significant differences occurred. Significance was accepted at the 95% confidence interval. All data presented in Figs. 1–4 and Tables 1–4 are expressed as means ± SD.

RESULTS

Baseline measurements of measured and calculated renal variables are shown in Table 1. GFR and RPF as well as V and electrolyte excretion rates were lower at 1 wk compared with 6 wk of life.

Effects of icatibant on GFR, RPF, and FF are illustrated in Fig. 1. GFR decreased by 20 min after icatibant in both age groups, returning toward control by 40 min in lambs aged 6 wk, but remaining decreased in 1-wk-old lambs. Because there were no effects of icatibant on RPF, FF mirrored GFR responses.

Effects of icatibant on V and electrolyte excretion rates are shown in Figs. 2 and 3. Administration of icatibant was associated with significant decreases in urinary flow, Cl−, and K+ excretion rates that were similar in both groups of lambs. In 6-wk-old lambs, Na+ excretion decreased at 20 min, returning toward control at 40 min, whereas Na+ excretion remained constant after icatibant administration to 1-wk-old lambs.

Table 2 shows the effects of icatibant on electrolyte clearances and fractional reabsorptions. Fractional Na+ reabsorption decreased transiently 40 min after icatibant administration to 1-wk-old lambs; there was a transient decrease at 20 min in 6-wk-old lambs. Fractional reabsorptions of Cl− and K+ remained constant after icatibant administration to both age groups of lambs (Table 2).

Effects of icatibant on tubular water handling are shown in Table 3. Urinary osmolalities and C\textsubscript{H2O} remained constant after icatibant administration to both age groups of lambs. There was a significant decrease in osmolar clearance after icatibant administration to both age groups (Table 3).

Table 1. Baseline renal measurements in conscious lambs

<table>
<thead>
<tr>
<th></th>
<th>1 wk Old</th>
<th>6 wk Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF, ml·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>2.16 ± 1.02</td>
<td>2.65 ± 0.53*</td>
</tr>
<tr>
<td>GFR, ml·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>0.44 ± 0.20</td>
<td>0.71 ± 0.20*</td>
</tr>
<tr>
<td>FF, %</td>
<td>23.2 ± 4.9</td>
<td>23.9 ± 4.7</td>
</tr>
<tr>
<td>V, ml·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>0.011 ± 0.006</td>
<td>0.015 ± 0.010*</td>
</tr>
<tr>
<td>U\textsubscript{NaV}, µmol·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>0.24 ± 0.27</td>
<td>0.59 ± 0.43*</td>
</tr>
<tr>
<td>U\textsubscript{K}, µmol·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>0.69 ± 0.43</td>
<td>0.79 ± 0.45*</td>
</tr>
<tr>
<td>U\textsubscript{ClV}, µmol·g\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>0.76 ± 0.60</td>
<td>1.20 ± 0.60*</td>
</tr>
</tbody>
</table>

Values are means ± SD. RPF, renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction; V, urinary flow rate; U\textsubscript{NaV}, Na+ excretion; U\textsubscript{K}, K+ excretion; U\textsubscript{ClV}, Cl− excretion. *P < 0.05 compared with 6 wk.
icatibant. Hematocrit and hemoglobin levels increased within 20 min of icatibant administration to 6-wk-old lambs and remained above control levels at 60 min (Table 4).

**DISCUSSION**

To test the hypothesis that the effects of endogenously produced bradykinin on glomerular and tubular function are age dependent, physiological responses to administration of the specific B2-receptor antagonist icatibant were measured in conscious, chronically instrumented 1- and 6-wk-old lambs. Novel findings of our experiments are as follows. 1) In response to icatibant administration, there was an ~80% decrease in GFR at 20 min in 1-wk-old lambs that was sustained for 60 min; in 6-wk-old lambs, there was an ~70% decrease in GFR by 20 min, with control levels reached by 40 min. 2) Administration of icatibant was associated with a significant decrease in urinary flow, Cl\(^-\), and K\(^+\) excretion rates that were similar in both groups of lambs. 3) In 6- but not 1-wk-old lambs, Na\(^+\) excretion decreased 20 min after icatibant administration, returning toward control at 40 min. 4) PRA increased by 20 min after icatibant administration in both age groups; this effect was more pronounced and prolonged in 1-wk-old lambs. 5) Plasma levels of PGE increased after icatibant administration to 1- but not 6-wk-old lambs. 6) At 1, but not 6 wk, hematocrit and hemoglobin levels increased within 20 min of icatibant administration and remained above control levels at 60 min. These findings provide the first description of the physiological effects of endogenously produced bradykinin on renal function during postnatal maturation in conscious, undisturbed animals and support our hypothesis that bradykinin modulates glomerular and tubular function in an age-dependent manner.

In physiological studies in adult rats pretreated with deoxycorticosterone enantate to promote activity of the kallikrein-kinin system, 2-wk administration of icatibant did not alter blood pressure, renal hemodynamics, or glomerular ultrafiltration (14). Icatibant did, however, lower V by ~70%, Na\(^+\) excretion by ~54%, and K\(^+\) excretion by ~30% (14). The authors concluded that endogenous kinins regulate tubular water and Na\(^+\) handling, at least in the presence of an activated kallikrein-kinin system. Baseline GFR and RPF as well as renin mRNA and kidney ANG II levels were found to be unaltered in anesthetized rats chronically treated with icatibant for the first 3 wk of postnatal life (10) compared with saline controls. In anesthetized newborn rabbits, GFR was unaltered by 4-day chronic icatibant treatment, whereas renal vascular resistance was increased (28) compared with age-matched saline controls. The present experiments in conscious newborn and older sheep provide new information regarding acute effects of icatibant under normal physiological conditions, as well as evidence that endogenously produced kinins appear to modulate glomerular as well as tubular function during postnatal maturation.

In 6-wk-old animals, there was a reduction in GFR of ~70% within 20 min of administration of icatibant. Previously, we showed that 20 min after administra-
tion of icatibant (16) to 6-wk-old lambs there was a 21% increase in mean arterial pressure and a 26% increase in renal blood flow. Therefore, the decrease in GFR in older lambs occurs concomitantly with an increased renal perfusion pressure, which one would expect to promote rather than to prohibit GFR. The mechanism(s) underlying this decrease in GFR is not known and will require additional investigation. However, taking into consideration the determinants of single nephron GFR, the filtration coefficient (Kf), and net filtration pressure, it is possible to speculate on the possible mechanisms involved in initiating this marked decrease in GFR in response to icatibant. A decrease in Kf could result from removal of the vaso-dilatory effects of bradykinin on mesangial cell contractility, because B2-receptor binding is present within the glomerulus, at least in adult animals. For example, Tomita and Pisano (25) measured small but significant bradykinin binding in isolated glomeruli of the rabbit kidney, and Emond et al. (11) demonstrated the presence of B2 receptors on rat cultured mesangial cells. Although a marked decrease in Kf alone is theoretically possible, it is likely that this would be accompanied by significant alterations to the filtration barrier itself (e.g., inflammation) and accompanying proteinuria. It is unlikely that removal of endogenously produced bradykinin would elicit such marked changes to the glomerular capillary. Alternatively, a reduction in GFR after icatibant administration to 6-wk-old lambs could result from a decrease in net filtration pressure. Because there was no significant effect of icatibant on either plasma osmolality or effective RPF, it is unlikely that the transcapillary oncotic pressure gradient was altered by icatibant. It is, however, possible that icatibant administration was associated with a decrease in the hydrostatic pressure gradient across glomerular capillaries, thereby decreasing net filtration pressure resulting from a preferential afferent arteriolar constriction after removal of endogenously produced bradykinin. In support of this premise are the in vitro experiments in juxtamedullary arterioles microdissected from rat kidneys (17) providing evidence that B2 receptors are present in afferent arterioles. In addition, Yu et al. (32) showed that the dilator effect of bradykinin in isolated perfused rabbit afferent arterioles was mediated by the B2 receptor, since it was abolished in the presence of icatibant.

In 1-wk-old lambs, the reduction in GFR of ~80% within 20 min of icatibant administration was sustained for 60 min, whereas in older animals, control levels were readily restored. Our previous experiments provide evidence that this decrease in GFR in newborn lambs would have occurred in the absence of any changes in renal perfusion pressure, because mean arterial pressure and renal blood flow were not decreased by icatibant (16). Age-dependent changes in the localization of B2 receptors on mesangial cells,

### Table 2. Effects of icatibant on tubular handling of electrolytes in conscious lambs

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Control</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNa, ml/min</td>
<td>6 0.09 ± 0.10†</td>
<td>0.03 ± 0.03*</td>
<td>0.07 ± 0.09†</td>
<td>0.08 ± 0.09†</td>
</tr>
<tr>
<td>FRNa, %</td>
<td>6 99.4 ± 0.6</td>
<td>98.9 ± 0.5*</td>
<td>98.9 ± 0.4</td>
<td>98.9 ± 0.4</td>
</tr>
<tr>
<td>CCl, ml/min</td>
<td>6 0.34 ± 0.27†</td>
<td>0.05 ± 0.07*</td>
<td>0.15 ± 0.18†</td>
<td>0.20 ± 0.16†</td>
</tr>
<tr>
<td>KCl, ml/min</td>
<td>6 0.55 ± 0.26</td>
<td>0.16 ± 0.08*</td>
<td>0.44 ± 0.20</td>
<td>0.43 ± 0.14</td>
</tr>
<tr>
<td>FRK, %</td>
<td>6 97.9 ± 1.9</td>
<td>98.4 ± 1.4</td>
<td>97.8 ± 0.9</td>
<td>98.9 ± 0.4</td>
</tr>
<tr>
<td>Ck, ml/min</td>
<td>6 98.4 ± 0.8</td>
<td>98.0 ± 1.1</td>
<td>98.4 ± 0.4</td>
<td>98.7 ± 0.4</td>
</tr>
<tr>
<td>UNa:UK</td>
<td>0.35 ± 0.43</td>
<td>0.71 ± 0.49</td>
<td>0.99 ± 0.64</td>
<td>0.61 ± 0.47</td>
</tr>
</tbody>
</table>

Values are means ± SD. CNa, Ck, CCl, Na, K, and Cl clearances, respectively. FRNa, FRK, FRCl, Na, K, and Cl tubular fractional reabsorptions, respectively. *P < 0.05 compared with control; †P < 0.05 compared with 6-wk-old lambs.

### Table 3. Effects of icatibant on tubular water handling in conscious lambs

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Control</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uosmol, mosmol/kgH2O</td>
<td>1 378 ± 459</td>
<td>393 ± 175</td>
<td>359 ± 153</td>
<td>345 ± 136</td>
</tr>
<tr>
<td>CH2O, ml/min</td>
<td>6 440 ± 349</td>
<td>421 ± 369</td>
<td>364 ± 172</td>
<td>314 ± 127</td>
</tr>
<tr>
<td>CosM, ml/min</td>
<td>1 -0.11 ± 0.23</td>
<td>-0.07 ± 0.06</td>
<td>-0.09 ± 0.11</td>
<td>-0.05 ± 0.11</td>
</tr>
<tr>
<td>6 -0.04 ± 0.45</td>
<td>-0.02 ± 0.08</td>
<td>-0.08 ± 0.25</td>
<td>-0.02 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>USMolar, Posmol</td>
<td>1 0.64 ± 0.39†</td>
<td>0.17 ± 0.15*</td>
<td>0.28 ± 0.31†</td>
<td>0.37 ± 0.27†</td>
</tr>
<tr>
<td>6 0.80 ± 0.37</td>
<td>0.20 ± 0.12*</td>
<td>0.56 ± 0.32*</td>
<td>0.56 ± 0.26*</td>
<td></td>
</tr>
<tr>
<td>Uosmol:Posmol</td>
<td>1 1.35 ± 0.59</td>
<td>1.33 ± 0.94</td>
<td>1.23 ± 0.59</td>
<td>1.11 ± 0.49</td>
</tr>
<tr>
<td>6 1.09 ± 0.72</td>
<td>0.93 ± 0.30</td>
<td>1.07 ± 0.48</td>
<td>0.99 ± 0.44</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Uosmol, urinary osmolality; CH2O, free water clearance; CosM, osmolar clearance; USMolar:Uosmol, urinary-to-plasma osmolality ratio. *P < 0.05 compared with control; †P < 0.05 compared with 6-wk-old lambs.

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Table 4. Effects of icatibant on plasma and whole blood measurements

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Control</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNa, mmol/l</td>
<td>1</td>
<td>143 ± 2</td>
<td>143 ± 2*</td>
<td>143 ± 2†</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>144 ± 3</td>
<td>145 ± 2</td>
<td>146 ± 3*</td>
</tr>
<tr>
<td>PK, mmol/l</td>
<td>1</td>
<td>3.9 ± 0.1†</td>
<td>3.7 ± 0.4*</td>
<td>3.6 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3.6 ± 0.3</td>
<td>3.7 ± 0.4</td>
<td>3.6 ± 0.4*</td>
</tr>
<tr>
<td>PCl, mmol/l</td>
<td>1</td>
<td>108 ± 5</td>
<td>111 ± 4</td>
<td>111 ± 4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>111 ± 7</td>
<td>111 ± 5</td>
<td>110 ± 5</td>
</tr>
<tr>
<td>Posmol, mosmol/kgH2O</td>
<td>1</td>
<td>293 ± 4</td>
<td>294 ± 4</td>
<td>293 ± 4†</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>295 ± 4</td>
<td>296 ± 3</td>
<td>296 ± 3</td>
</tr>
<tr>
<td>Hct, %</td>
<td>1</td>
<td>28.2 ± 1.5</td>
<td>26.4 ± 4.2†</td>
<td>28.1 ± 1.8†</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>27.1 ± 5.1</td>
<td>34.5 ± 4.6*</td>
<td>34.1 ± 5.5*</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>1</td>
<td>10.4 ± 0.6†</td>
<td>10.9 ± 0.7*</td>
<td>11.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8.9 ± 1.5</td>
<td>11.5 ± 2.8*</td>
<td>11.2 ± 2.6*</td>
</tr>
</tbody>
</table>

Values are means ± SD. PNa, PK, and PCl, plasma concentrations of Na, K, and Cl; Hb, hemoglobin; Hct, hematocrit. *P < 0.05 compared with control; †P < 0.05 compared with 6-wk-old lambs.
nal sides of the tubular epithelial cells, was associated with an increase in renin secretion. The renin responses to icatibant in 1- and 6-wk-old lambs occurred concomitantly with changes in GFR and, therefore, are probably secondary to the effects of icatibant in reducing Na\(^+\) delivery to the macula densa cells of the juxtaglomerular apparatus rather than the result of direct effects of locally produced bradykinin on renin release. Because ANG II is a physiological modulator of PGE biosynthesis, it also seems likely that activation of the renin-angiotensin system after icatibant administration promoted the biosynthesis of PGE in 1-wk-old lambs. Consistent with this suggestion is the fact that PGE levels remained elevated at 60 min, at which time PRA remained elevated above control levels.

In previous experiments by Tóth-Heyn and Guignard (27), acute effects of 300 \(\mu\)g/kg of icatibant administered subcutaneously on various parameters of renal function were measured in pentobarbital sodium-anesthetized and artificially ventilated newborn rabbits (27). There was no apparent effect of acute administration of icatibant on GFR in anesthetized newborn rabbits, whereas renal vascular resistance was increased by \(\sim\)10% and V was increased by \(\sim\)50% (27). These findings are in direct contrast to our observed effects of a decrease in GFR and V in conscious young lambs after acute icatibant administration. Species differences (sheep vs. rabbits), mode of delivery of icatibant (intravenous vs. subcutaneous), and dose (12.5 vs. 300 \(\mu\)g/kg) could perhaps account for these differences. However, the data obtained in the aforementioned experiments in anesthetized rabbits should be interpreted with caution given the known deleterious effects of surgery and anesthesia on cardiovascular and renal function (1, 15, 20, 21, 30).

In summary, our experiments provide new information that administration of the specific B\(_2\)-receptor antagonist icatibant to conscious lambs results in age-dependent changes in glomerular ultrafiltration, FF, and tubular Na\(^+\) reabsorption. Therefore, our data provide new information regarding the renal effects of endogenously produced kinins during postnatal maturation under normal physiological conditions.

**Perspectives**

In all species studied to date, including the human, postnatal maturation is associated with a marked decrease in renal vascular resistance resulting in an increased renal perfusion pressure and GFR. In addition, maturational changes in tubular function of the various nephron segments occur. These maturational renal changes are complex and likely result from an interaction between various neurohumoral factors that are developmentally regulated, in combination with age-dependent alterations in the activity of various systems. The present findings allow us to incorporate the role of endogenously produced bradykinin into this complex maturational profile. Bradykinin does not appear to mediate changes in renal vascular tone during postnatal maturation but does modulate both GFR and tubular function in an age-dependent manner. Endogenously produced bradykinin through its dilator effect of activation of B\(_2\) receptors on mesangial cells and/or pregglomerular vessels normally promotes ultrafiltration. In addition, bradykinin appears to modulate Na\(^+\) reabsorption in the distal nephron later in life, although not soon after birth, again probably reflecting age-dependent changes in the localization of B\(_2\) receptors in specific nephron segments. Of particular future importance will be the determination of B\(_2\)-receptor binding in the ovine kidney during maturation as well as the potential interactions between bradykinin, ANG II, and PGs in modulating renal function during maturation.

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