

# Pregnant Rats Treated With a Serotonin Precursor Have Reduced Fetal Weight and Lower Plasma Volume and Kallikrein Levels

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**Abstract**—Pregnant women with preeclampsia have increased serotonin levels, suggesting a possible role of this amine in abnormal pregnancy. With the hypothesis that an increase in serotonin would reduce volume expansion and cause fetal growth restriction, we evaluated the maternal and fetal effects of the administration of the serotonin precursor 5-hydroxytryptophan (5-HTP) to Sprague-Dawley rats. At pregnancy day 13 (n=19) or in random cycle nonpregnant rats (n=10), animals were assigned to a single injection of 5-HTP (100 mg/kg IP) or to a control group. Animals were studied at day 21, after overnight urinary collection. Additional pregnant rats received ketanserin (1 mg/kg), a 5-HT<sub>2</sub> receptor antagonist, 1 hour before 5-HTP injection. In pregnant rats, 5-HTP lowered plasma volume (control: 22±1.1; 5-HTP: 17±0.7 mL;  $P<0.001$ ) and creatinine clearance, whereas serum creatinine and urinary protein excretion were increased; no changes were observed in nonpregnant rats. Systolic blood pressure did not change significantly. Urinary kallikrein activity and plasma aldosterone levels decreased only in pregnant animals. Fetal (control: 5.5±0.1; 5-HTP: 4.2±0.2 g;  $P<0.001$ ) and placental weights were reduced. In nonpregnant and pregnant animals, 5-HTP caused profound renal morphological alterations and decreased kallikrein immunostaining. Preadministration of ketanserin abolished all of the changes associated with the use of 5-HTP. These data indicate that the administration of a serotonin precursor to pregnant rats limits plasma volume expansion and fetal growth via 5-HT<sub>2</sub> receptors, suggesting a possible role for serotonin in abnormal pregnancy. We postulate that an increased vascular resistance, both at the placental and renal levels, mediates these effects. (*Hypertension*. 2007;50:773-779.)

**Key Words:** preeclampsia/pregnancy ■ experimental models ■ acute kidney failure ■ kallikrein ■ aldosterone ■ plasma volume ■ serotonin

Normal pregnancy, in humans and other mammals, is characterized by a significant reduction in systemic vascular resistance associated with lower arterial blood pressure, increased cardiac output, stimulation of the renin-angiotensin system, and plasma volume expansion.<sup>1–3</sup> These changes cause an important increment in uteroplacental blood flow, allowing normal fetal growth.

In previous studies we have observed that pregnancy complications, such as fetal growth restriction or preeclampsia, are associated with reduced plasma volume expansion, increased vascular resistance, and lower levels of plasma renin activity, plasma aldosterone, and urinary kallikrein activity.<sup>4,5</sup> In preeclampsia an increased platelet aggregation has been described, with a consequent increment in serotonin (5-hydroxytryptamine; 5-HT) levels.<sup>6</sup> Serotonin is an endogenous amine synthesized by the enzymes tryptophan hydroxylase and decarboxylase from 5-hydroxytryptophane (5-HTP)

and is metabolized by the enzyme monoamino-oxidase A to 5-hydroxyindole-3-acetic acid.<sup>7</sup> Serotonin has multiple cardiovascular effects, causing either blood vessel dilation through its 5-HT<sub>1</sub> receptor or constriction via the 5-HT<sub>2</sub>-receptor. The differential distribution of these receptor subtypes in various vascular beds most probably explains the different vascular responses observed after serotonin administration. In the uteroplacental circulation, including chorionic vessels, there is predominance of 5-HT<sub>2</sub> receptors, and serotonin increases uteroplacental resistance.<sup>8–10</sup>

Consequently, our hypothesis is that the administration of a serotonin precursor to pregnant rats would alter renal function, reduce volume expansion, and cause fetal growth restriction. To test this hypothesis, in the present study we explored the maternal and fetal effects of a single dose of 5-HTP administered to pregnant rats at a time of maximal renal vasodilation. In addition, we were interested in deter-

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**Table 1. Maternal Parameters in Nonpregnant and Pregnant Rats After 5-HTP Administration (Day 14 of Pregnancy)**

Parameter	Nonpregnant		Pregnant	
	Control (n=7)	5-HTP (n=7)	Control (n=5)	5-HTP (n=6)
Systolic BP, mm Hg	107±4.8	104±4.8	110±4.8	113±8.8
Hematocrit, %	0.41±0.01	0.40±0.02	0.38±0.01	0.39±0.01
Renal weight, g/100 g net weight	0.46±0.02	0.56±0.02*	0.45±0.01	0.54±0.03*
Urine volume, mL/16 hours	5.9±2.2	14.5±1.6*	3.0±0.9	16.1±2.3*
Serum creatinine, mg/dL	0.56±0.02	2.5±0.4*	0.4±0.03	2.0±0.3*
Creatinine clearance, mL/min	1.2±0.1	0.3±0.1*	1.3±0.1	0.4±0.1*
Urinary protein, mg/16 hours	0.9±0.4	13±4.0*	3.9±2.4	24.7±5.2*†
Urinary kallikrein activity, nmol/16 hours	744±256	51±23.5*	803±118	56±38*

Values represent the mean±SEM.

\*Differences between control and 5-HTP; †Differences between nonpregnant and pregnant rats;  $P<0.05$ , ANOVA.

mining differences in the response between nonpregnant and pregnant rats.

## Methods

### Experimental Design

Female Sprague-Dawley rats (220 to 250 g in initial weight) were maintained in a controlled environment at the Center for Medical Research animal care facilities. The protocols used met the international guidelines for animal welfare and the institutional review board of the School of Medicine approved them. Estrous cycles were monitored by daily vaginal smears, and rats were randomly assigned to nonpregnant or pregnant groups. Sperm-positive day was considered as day 0. All of the rats had free access to standard rat chow and tap water throughout the study period. At day 13 of pregnancy or in the corresponding day in nonpregnant rats, animals were randomized to a 5-HTP group, which received a single injection of 100 mg/kg IP dissolved in 0.5 mL of saline solution or to a control group that received the same volume of saline IP, also only once. This dose was chosen after preliminary experiments in nonpregnant animals in which we observed that, with a lower dose (50 mg/kg as a single dose), only 50% of the rats exhibited signs of renal failure, whereas with a higher dose (200 mg/kg), there was increased mortality. A subgroup of these rats was placed in metabolic cages with free access to food and water from 5 PM to 9 AM of day 14 (nonpregnant control: 7; nonpregnant 5-HTP: 7; pregnant control: 5; pregnant 5-HTP: 6), whereas the remaining rats were studied at day 21 (nonpregnant control: 5; nonpregnant 5-HTP: 5; pregnant control: 9; pregnant 5-HTP: 10). Systolic blood pressure was measured by tail-cuff plethysmography after urine collection was completed. The rats were then anesthetized with xylazine (5 mg/kg) plus ketamine (40 mg/kg IP), plasma volume was measured by the Evans blue dye dilution technique as described elsewhere,<sup>11</sup> (only in day 21 rats) and blood samples were obtained from the abdominal aorta. An aliquot was used for microhematocrit determination, the remainder was centrifuged, and the plasma was frozen for further determinations. Sixteen-hour urine was measured, aliquoted, and stored frozen until analyzed as described.<sup>11</sup> Litter size and the weight of the whole uterine content (day 14 dams) or individual weights of fetuses and placentas (day 21 dams) were recorded.

Additional pregnant rats were treated with ketanserin (1 mg/kg IP), a 5-HT<sub>2</sub> receptor antagonist, administered as a single injection at day 13, 1 hour before 5-HTP or saline administration. These animals were studied at day 21, following the same procedure described above (n=4 per group). In preliminary experiments with nonpregnant animals, we determined the dose of the antagonist that completely blocked the renal effects of 5-HTP. To explore placental conversion and/or passage of 5-HTP to the uteroplacental circulation, we measured 5-HTP and 5-HT in amniotic fluid.

### Tissue Processing and Immunohistochemistry

Kidneys were weighted, sliced, and fixed in Bouin's solution; embedded in Paraplast; serially sectioned at 7-μm thickness; and mounted on glass slides for hematoxylin-eosin staining and immunohistochemistry. Immunohistochemical staining for renal kallikrein was performed according to the peroxidase/antiperoxidase method as described previously.<sup>12</sup> Controls for the immunostaining procedure were prepared by omission of the first antibody or by its replacement with preimmune serum. The tissue samples from all of the groups were coded and studied independently by 2 observers (S.P.S. and W.R.) in a blinded fashion, 1 section selected at random was used for each rat, and ≥4 fields per section were studied.<sup>12,13</sup> To estimate the intensity of the immunostaining at the cellular level, the observers made a single ordinal ranking (0 to 3), with 0 being absent, 1 being very faint yet distinguishable, 2 being moderate staining, and 3 the strongest staining.<sup>12</sup>

### Hormonal and Biochemical Measurements

Plasma aldosterone was measured by radioimmunoassay, with the use of a commercial kit from Diagnostic Products Corporation. Urinary kallikrein activity was determined by the amidase method,<sup>14</sup> with the use of synthetic substrate DL-Val-Leu-arginine-p-nitroanilide (Sigma). Plasma and urinary creatinine levels were measured with a Beckman Autoanalyzer. 5-HTP and 5-HT were determined by high-performance liquid chromatography as described elsewhere.<sup>15</sup> Urinary protein concentration was determined by the Bradford method (Bio-Rad protein assay). Ketanserin and 5-HTP were obtained from Sigma Chemical Co.

### Statistical Analysis

Statistical analysis was performed by ANOVA or by an unpaired 2-tailed Student's *t* test, using the computer program Stat View II (Abacus Concepts Inc). Statistical significance was accepted at a level of  $P<0.05$ . All of the data were expressed as mean±SEM.

## Results

### Blood Pressure, Renal, and Hormonal Changes After a Single Injection of 5-HTP

Acute effects of a single injection of 5-HTP are shown in Table 1. Systolic blood pressure and hematocrit levels remained unchanged, whereas nonpregnant and pregnant 5-HTP-treated rats exhibited increased renal weight, high urine volume and serum creatinine, and reduced creatinine clearance and urinary kallikrein activity. Urinary protein excretion increased, particularly in pregnant rats.

**Table 2. Maternal Weight and Renal Function in Nonpregnant and Pregnant Rats 1 Week After 5-HTP Administration (Day 21 of Pregnancy)**

Parameter	Nonpregnant		Pregnant	
	Control (n=5)	5-HTP (n=5)	Control (n=9)	5-HTP (n=10)
Initial weight, g	230±2.0	234±3.0	229±6.0	229±6.0
Weight gain, g	23.6±4.79	18.6±3.9	128±8.4†	61±9.8*†
Net weight, g	200±3.9	192±5.0	212±4.8	182±6.4*
Renal weight, g/100 g net weight	0.4±0.03	0.6±0.05*	0.4±0.02	0.9±0.04*†
Water intake, mL/16 hours	27.6±1.7	31.2±5.9	29.1±2.5	32.1±4.4
Urine volume, mL/16 hours	4.0±0.92	8.6±2.7*	5.3±1.0	10.3±1.3*
Serum creatinine, mg/dL	0.42±0.08	0.58±0.05	0.49±0.05	0.77±0.06*†
Creatinine clearance, mL/min	1.5±0.2	1.2±0.1	1.7±0.1	1.0±0.12*
Urinary protein, mg/16 hours	2.8±1.5	7.2±5.1	3.1±1.1	13.1±4.4*

Values represent the mean±SEM.

\*Differences between control and 5-HTP; †Differences between nonpregnant and pregnant rats;  $P<0.05$ , ANOVA.

Main changes observed 1 week after a single injection of 5-HTP are shown in Table 2. Initial weight was similar in all of the groups. As expected, weight gain was higher in pregnant than in nonpregnant rats. The administration of 5-HTP significantly reduced weight gain and net weight in pregnant rats but did not modify weight in the nonpregnant animals. Water intake was similar in all of the groups. Renal weight and urine volume were significantly increased by 5-HTP injection in nonpregnant and pregnant rats. At day 21, only pregnant rats treated with 5-HTP continued to exhibit high serum creatinine and protein excretion and lower creatinine clearance; nonpregnant 5-HTP-treated rats had levels similar to controls.

At day 21 of pregnancy, systolic blood pressure and hematocrit levels were reduced by pregnancy and were unaffected by 5-HTP. Plasma volume levels were increased by pregnancy and reduced by 5-HTP only in pregnant rats. Both groups of pregnant rats had significantly higher plasma aldosterone levels than the corresponding nonpregnant groups; 5-HTP reduced aldosterone only in the pregnant animals. Similarly, at day 21, only pregnant rats had a significant reduction in urinary kallikrein activity (Table 3). When kallikrein activity was expressed per urinary creatinine excretion, this difference remained significant (nonpregnant control:  $1.5\pm0.1$ , nonpregnant 5-HTP:  $0.8\pm0.35$ ,  $P<0.05$ ;

pregnant control:  $1.5\pm0.07$ , pregnant 5-HTP:  $0.33\pm0.04$  nmol/mg,  $P<0.001$ ).

### Fetal Effects of 5-HTP Injection

Pregnant rats treated with 5-HTP had reduced litter size (control:  $10.7\pm0.9$ ; 5-HTP:  $6.9\pm1.3$ ;  $P<0.05$ ), increased fetal reabsorptions (control:  $0.4\pm0.4$ ; 5-HTP:  $5.1\pm1.6$ ;  $P<0.01$ ), and reduced fetal (control:  $5.5\pm0.1$ ; 5-HTP:  $4.2\pm0.2$  g;  $P<0.001$ ) and placental weights (control:  $0.5\pm0.02$ ; 5-HTP:  $0.4\pm0.01$  g;  $P<0.01$ ). Administration of 5-HTP increased 5-HTP in the amniotic fluid at day 14 (control:  $20.4\pm17.5$ ; 5-HTP:  $215\pm75$  ng/mL;  $P<0.05$ ), but at day 21 this difference was not statistically significant (control:  $6.5\pm5.5$ ; 5-HTP:  $33\pm15$  ng/mL). 5-HT also increased in amniotic fluid and remained elevated until term (control:  $5.0\pm3.0$ ; 5-HTP:  $26.0\pm3$  ng/mL;  $P<0.01$ ).

### Morphological Study

Macroscopic examination of kidneys from 5-HTP rats, either at day 14 or 21, revealed a fine white punctuate, compatible with renal ischemia, which was present in every treated rat. Neither the liver nor the heart exhibited these macroscopic changes. Kidneys from 5-HTP rats exhibited histologic alterations compatible with acute renal necrosis, which were already present 24 hours after drug injection. These abnormalities were observed in all of the treated

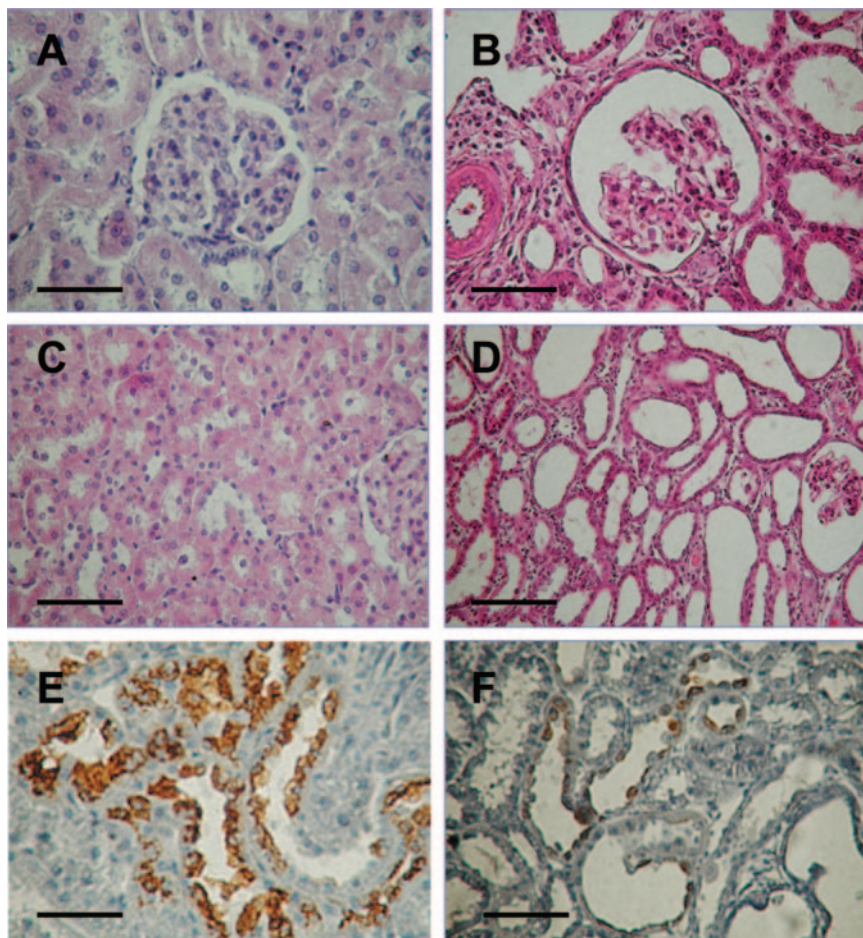
**Table 3. Blood Pressure, Plasma Volume, Hematocrit, and Hormonal Changes in Nonpregnant and Pregnant Rats 1 Week After 5-HTP Administration (Day 21 of Pregnancy)**

Parameter	Nonpregnant		Pregnant	
	Control (n=5)	5-HTP (n=5)	Control (n=9)	5-HTP (n=10)
Systolic BP, mm Hg	120±4.5	121±4.5	95.7±5.2†	103±3.8†
Hematocrit	0.39±0.007	0.37±0.005	0.31±0.01†	0.32±0.01†
Plasma volume, mL	15.0±0.4	14.1±0.5	22.0±1.2†	17.0±0.7*†
Plasma aldosterone, pg/mL	164±23.7	134±405	1694±203†	1045±184*†
Urinary kallikrein activity, nmol/16 hours	803±102	408±104	1297±189†	232±51*

Values represent the mean±SEM.

\*Differences between control and 5-HTP; †Differences between nonpregnant and pregnant rats;  $P<0.05$ , ANOVA.





**Figure.** Color plate showing representative morphological features of renal sections from control and 5-HTP-treated rats, obtained at day 21 of pregnancy. Sections from control (A and C) and 5-HTP-treated rats (B and D) stained with hematoxylin and eosin depicting normal glomerular structure in A and gross glomerular alterations in B. C and D are sections obtained at the tubular level. Note the atrophy of tubules in D. E and F, Sections from control (E) and 5-HTP-treated (F) rats immunostained for kallikrein. Kallikrein is present in connecting tubules, which are dilated and atrophic, and with reduced kallikrein staining in 5-HTP rats. Bar=40  $\mu$ m.

rats, either nonpregnant or pregnant. The alteration in the renal architecture persisted at day 21, at a time when kidneys from treated rats exhibited gross distal tubule dilation, tubules with hyaline material, interstitial inflammatory infiltrate, and glomerular atrophy. Representative renal tissue sections from control (A, C, and E) and 5-HTP-treated rats (B, D, and F) at day 21 of pregnancy are shown in the Figure panels A and C and show normal glomerular and tubular regions from a control pregnant rat. The Figure, panel B shows a section from a 5-HTP rat, depicting abnormal glomerular structure, whereas the Figure, panel D shows dilatation of some tubules and flattening of the tubular epithelium. Kallikrein immunostaining was observed exclusively in the connecting tubule cells of the distal nephron (Figure, panels E and F) and was reduced in 5-HTP rats (Figure, panel F). Compared with control rats, kallikrein-containing cells from 5-HTP rats were smaller, and the connecting tubules appeared dilated and atrophic. Semiquantitative analysis of staining intensity revealed that 7 of 10 control rats exhibited the maximum staining, scoring +++, and 3 had moderate staining (++). None of the 5-HTP treated rats exhibited maximum store; 2 had moderate staining, scoring ++; and the remaining exhibited faint staining, scoring +.

#### Ketanserin Effects

The effects of ketanserin injection 1 hour before 5-HTP were evaluated at day 21 of pregnancy. Ketanserin had no effect in

control pregnant rats. In the 5-HTP-treated rats, ketanserin reduced serum creatinine levels (5-HTP:  $0.77 \pm 0.06$ ; 5-HTP+ketanserin:  $0.48 \pm 0.03$  mg/dL;  $P < 0.01$ ) and increased creatinine clearance (5-HTP:  $0.98 \pm 0.1$ ; 5-HTP+ketanserin:  $2.3 \pm 0.2$  mL/min;  $P < 0.001$ ), reaching values similar to those of control rats. Plasma volume (5-HTP:  $17 \pm 0.7$ ; 5-HTP+ketanserin:  $23.2 \pm 0.5$  mL;  $P < 0.001$ ) and urinary kallikrein activity (5-HTP:  $232 \pm 5.1$ ; 5-HTP+ketanserin:  $1316 \pm 212$  nmol per 16 hours;  $P < 0.001$ ) reached normal levels with ketanserin pretreatment. Similarly, litter size (5-HTP:  $6.9 \pm 1.3$ ; 5-HTP+ketanserin:  $11.3 \pm 1.0$ ;  $P < 0.05$ ) and fetal weight (5-HTP:  $4.2 \pm 0.2$ ; 5-HTP+ketanserin:  $5.4 \pm 0.2$  g;  $P < 0.001$ ) increased. Renal histologic alterations were also prevented with ketanserin pretreatment.

#### Discussion

Present results indicate that the administration of 5-HTP, a serotonin precursor, to pregnant rats limits plasma volume expansion and reduces fetal growth. These alterations were abolished with previous administration of ketanserin, suggesting that they were mediated via 5-HT<sub>2</sub> receptors. In addition, pregnant rats treated with 5-HTP had greater reductions in urinary kallikrein activity and in renal function than nonpregnant animals.

Pregnancy is characterized by important hemodynamic changes, including increased cardiac output, plasma volume

expansion, and reduced systemic vascular resistance, which contribute to an adequate blood supply to the uteroplacental territory.<sup>1,2</sup> To achieve positive sodium balance and volume expansion, important changes in renal function during pregnancy, such as a rise in glomerular filtration rate and in renal plasma flow, should take place.<sup>16–18</sup> This rise in renal plasma flow is secondary to significant reductions in both the renal afferent and efferent arteriolar resistances.<sup>18</sup> In the rat, the greatest changes in effective renal plasma flow and in glomerular filtration rate occur at midpregnancy, at the time when we administered the serotonin precursor. 5-HTP caused abnormal renal function, which was of greater magnitude in pregnant than in nonpregnant rats. In addition, 5-HTP produced severe renal morphological alterations. The fact that serotonin may induce renal cortical necrosis in the rat was described long time ago,<sup>19</sup> and in 1955 Page postulated serotonin as the vasoconstrictor substance responsible for renal cortical necrosis as seen in pregnant patients after placental abruption as reviewed in Reference 20. Other authors have characterized the progress of serotonin-induced renal lesions that include an initial ischemic tubular necrosis, followed by dilatation and atrophy of the tubules,<sup>21</sup> which are alterations similar to our findings. In the rat kidney, vasoconstriction-inducing 5-HT<sub>2</sub> receptors have been described in arcuate and interlobar arteries, whereas 5HT<sub>1</sub> receptors present in afferent and efferent arterioles and in the glomeruli cause vasodilation.<sup>22</sup> Considering that we used a 5-HTP dose that did not modify blood pressure, the renal changes were likely caused by a selective vasoconstrictor effect in the renal vasculature. The abolishment of kidney damage by previous administration of ketanserin suggests that it was mediated via 5-HT<sub>2</sub> receptors.

We also observed that pregnant but not nonpregnant rats treated with the serotonin precursor had a limited volume expansion when compared with the corresponding control rats. Several factors can contribute to this inadequate volume expansion. Although both groups of pregnant rats increased aldosterone levels when compared with nonpregnant animals, this increment was reduced by 5-HTP injection. Aldosterone is a major determinant of sodium balance in pregnancy, opposing the natriuretic effects of progesterone and atrial natriuretic factor.<sup>1,23</sup> Aldosterone levels are markedly increased in normal pregnancy<sup>24</sup> but decreased in pregnancies complicated with preeclampsia or fetal growth restriction.<sup>5,25</sup> Second, abnormal volume expansion can be caused by an impaired renal water-retaining ability associated with renal injury, because urine output was significantly increased and renal function decreased by 5-HTP treatment. Interestingly, we demonstrated previously that pregnant rats with chronic renal failure caused by 5/6 nephrectomy are able to develop normal volume expansion and adequate fetal growth,<sup>26</sup> suggesting the existence of compensatory mechanisms that are set in motion some time after renal failure starts.

In this study, we demonstrated that the administration of 5-HTP caused a significant reduction in renal kallikrein expression and in urinary kallikrein activity, either when expressed in absolute values or when corrected per creatinine excretion. The renal kallikrein-kinin system is activated in normal pregnancy and reduced in pregnant women with PE or

fetal growth restriction and in several animal models associated with reduced fetal growth.<sup>4,5,12,14</sup> Previous studies have provided evidence that the kallikrein-kinin system participates in the regulation of blood pressure, in the control of extracellular volume, and in renal function.<sup>27,28</sup> The reduction in kallikrein activity observed in the present study is compatible with the structural abnormalities observed in the connecting tubule cells. These alterations resemble those described previously after NO synthase inhibition, which also caused reduced kallikrein excretion.<sup>12</sup> However, we cannot rule out the possibility that serotonin, per se, or indirectly through its vascular effects, may alter kallikrein synthesis. Taken together, the alterations in kallikrein activity, changes in glomerular filtration rate, and reduction in hematocrit independent of volume expansion may be caused by renal injury and secondary abnormal erythropoiesis, a possibility that was not explored in the present study. It is worth noting that hematocrit values were not significantly different between both pregnant groups despite their differences in plasma volume, suggesting that other factors influence the red blood cell mass:plasma ratio. It is interesting to note that previous studies have shown that in, normal humans, the infusion of 5-HTP produced marked increases in the urinary excretion of 5-HTP and 5-HT, without significant changes in blood 5-HT levels, suggesting renal conversion of 5-HTP to 5-HT.<sup>29</sup> This would explain the intense renal compromise without alterations in other maternal organs.

The injection of the serotonin precursor caused fetal growth restriction, lower placental weight, and increased fetal reabsorption. Several studies, in human and in pregnant animals, have demonstrated that a reduced volume expansion during pregnancy leads to a reduced cardiac output and significant reduction in uteroplacental blood flow that alter the normal fetal growth.<sup>4,5,30,31</sup> Nevertheless, it is reasonable to speculate that, in addition to the systemic hemodynamic changes, serotonin caused important local effects. Serotonin has a marked vasoconstrictor effect on umbilical and chorionic arteries, suggesting that it may play a role in the regulation of placental blood flow.<sup>32,33</sup> In addition, serotonin receptors have been found in several reproductive organs, including normal human placental tissue.<sup>34,35</sup> Rats treated with 5-HTP had elevated serotonin levels in amniotic fluid, indicating that either 5-HTP is metabolized at this level and/or that serotonin crosses the placental barrier. In this regard, the mRNA for the serotonin transporter has been detected in the chorionic villa of human placenta.<sup>36</sup>

Several lines of evidence have implicated serotonin as a mediator in the genesis of preeclampsia. Plasma serotonin concentration and the urinary excretion of serotonin metabolites are increased in preeclamptic women and the catalytic efficiency of the expressed monoamine oxidase-A, the major factor in the regulation of serotonin levels in pregnancy, is reduced in preeclamptic placenta.<sup>20,37,38</sup> In a model of spontaneous pregnancy-induced hypertension and intrauterine growth restriction in rats, placentas from these hypertensive rats displayed altered expression of several genes of which the protein products have been implicated in preeclampsia, including serotonin receptor.<sup>39</sup> It is worth noting that, at the dose used, 5-HTP did not alter the normal blood pressure—



lowering effect that is characteristic of near-term pregnancy in the rat, providing the opportunity to separate systemic from local vasoconstrictor effects. This lack of systemic vasoconstrictor effect was also present at day 14 of pregnancy. Similar findings have been demonstrated in the pregnant sheep, in which systemic infusions of serotonin in third-trimester pregnant ewes produced uterine vasoconstriction with limited cardiovascular systemic response (for review see Reference 20).

Ketanserin is a 5-HT<sub>2</sub> receptor antagonist that produces a selective inhibition of serotonin-induced vasoconstriction, and it has been used to treat preeclampsia.<sup>40,41</sup> In the present study, the previous administration of ketanserin completely prevented the maternal and fetal effects associated with 5-HTP injection, thus suggesting that 5-HTP produced its effects via 5-HT<sub>2</sub> receptors. Normalization of all of the alterations produced by 5-HTP injection with ketanserin indicates that, in conditions of increased levels of endogenous serotonin, as in preeclampsia, this drug may have additional beneficial effects other than blood pressure normalization.

## Perspectives

In the present study, we demonstrated that the administration of the serotonin precursor 5-HTP to pregnant rats caused significant reductions in fetal weight and volume expansion, associated with lower kallikrein and aldosterone levels. In addition, it produced significant morphological and functional renal alterations, which were more pronounced in pregnant rats. These data suggest that an excess of the endogenous vasoconstrictor serotonin, as observed in some pregnancy conditions such as preeclampsia, could contribute to abnormal pregnancy outcome. It is of interest that ketanserin, a drug used previously in treating preeclamptic women, had an important beneficial effect in pregnancy outcome not mediated through blood pressure reduction. Thus, ketanserin may prevent some of the abnormalities associated with preeclampsia acting at both placental and renal levels.

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## Disclosures

None.

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## Pregnant Rats Treated With a Serotonin Precursor Have Reduced Fetal Weight and Lower Plasma Volume and Kallikrein Levels

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