Mineralocorticoids participate in the reduced vascular reactivity of pregnant rats

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Provencher M, Houde V, Brochu M, St-Louis J. Mineralocorticoids participate in the reduced vascular reactivity of pregnant rats. Am J Physiol Heart Circ Physiol 302: H1195–H1201, 2012. First published December 23, 2011; doi:10.1152/ajpheart.00510.2011.—The renin-angiotensin-aldosterone (RAA) system is markedly activated in pregnancy. We evaluated if mineralocorticoid receptors (MR), a major component of the RAA system, are involved in the reduced vascular reactivity associated with pregnancy. Canrenoate (MR antagonist; 20 mg·kg⁻¹·day⁻¹) was administered to nonpregnant (NP) rats for 7 days and to pregnant rats from day 15 to 22 of gestation. These were killed on day 17, 19, or 22 of gestation and, for NP rats, after 7 days treatment. Constrictor responses to phenylephrine (PhE) and KCl were measured in endothelium-denuded thoracic aortic rings under the influence of modulators of potassium (activators) and calcium (blocker) channels. Responses to the constrictors were blunted from days 17 to 22 of gestation. Although canrenoate increased responses to PhE and KCl, it did not reverse their blunted responses in gestation. NS-1619 and cromakalim (respectively, high-conductance calcium-activated potassium channels and ATP-sensitive potassium channel activators) diminished responses to both PhE and KCl. Inhibition by NS-1619 on responses to both agonists was decreased under canrenoate treatment in NP, but the reduced influence of NS-1619 during gestation was reversed by the mineralocorticoid antagonist. Cromakalim reduced the response to PhE significantly in the pregnant groups; this effect was enhanced by canrenoate. Finally, nifedipine (calcium channel blocker) markedly reduced KCl responses but to a lesser extent at the end of pregnancy, an inhibiting effect that was increased with canrenoate treatment. These data demonstrate that treating rats with a MR antagonist increased vascular reactivity but that it differentially affected potassium and calcium channel activity in aortas of NP and pregnant animals. This suggests that aldosterone is one of the components involved in vascular adaptations to pregnancy.

In pregnant rats, PRA is increased early in gestation while aldosterone levels raise from midpregnancy until term (7, 18). In conditions other than pregnancy, such increases of the RAA system are associated with hypertension. This renders paradoxical the role of heightened RAA system in pregnancy (36). We have reported that increasing the activity of the RAA system by giving rats a low-sodium diet during the last 7 days of gestation resulted in elevated PRA and plasma aldosterone levels but reduced plasma volume expansion compared with normal pregnancy. Moreover, the end of gestation decrease in BP was maintained (35). In contrast, when the RAA system was depressed by a high-sodium diet, pregnant rats manifested reduced PRA and aldosterone levels while the diminution of BP usually linked with pregnancy was eliminated (4). In addition, high-sodium intake during gestation was associated with the reversal of gestational-related resistance to vasopressors (3).

It has been documented that the activity of high-conductance calcium-activated potassium channels (BKCa) and ATP-sensitive potassium channels (KATP) is increased in vascular smooth muscle (VSM) of normal pregnant animals (9, 22, 24). It is considered that opening of potassium channels leads to hyperpolarization of vascular smooth muscle cells (VSMC), which results in delayed opening of voltage-dependent calcium channels (VDCC) and consequently reduces smooth muscle constriction (9). This is compatible with data denoting some impairment of calcium influx through VDCC in aortic rings of pregnant rats (34). Furthermore, pregnant rats on a high-sodium diet (decreased RAA system) display reduced KATP activity and increased BKCa and VDCC activities, affirming RAA system involvement in the ionic balance of VSMC (3).

Aldosterone plays a major role in electrolyte homeostasis in the kidneys and colon by controlling sodium reabsorption and potassium secretion (5, 43). Lately, studies have demonstrated the presence of mineralocorticoid receptors (MR) in nonepithelial tissues, including heart and blood vessels (42). Aldosterone was reported to contribute to vascular remodeling and endothelial dysfunction through several coupling mechanisms (8, 13, 23), all associated with heightened vascular tone. Paradoxically, the increase in aldosterone levels in pregnancy occurs together with decreased vascular resistance (10), indicating that gestation resets some of the physiological responses normally consequent to an enhanced RAA system. This paradoxical presence of the RAA system makes us believe that MR are key factors in the control of vascular reactivity during pregnancy. We hypothesize that aldosterone acts on VSM through the modulation of ion channel activity. To confirm this, nonpregnant (NP) and term-pregnant rats were treated for 7 days with a MR antagonist,
potassium canrenoate. The objective was to characterize vascular reactivity of the aorta from these animals in the absence or presence of potassium and calcium channel modulators. To do so, we took profit of earlier work from this laboratory that has shown that the use of thoracic aorta is a convenient in vitro preparation to study the vascular blunted responses to vasoconstrictors (3, 9, 34).

MATERIALS AND METHODS

Animals. The experimental procedures were reviewed and approved by the local Animal Care Committee, accredited by the Canadian Council on Animal Care. Female Sprague-Dawley rats (Charles River Canada, Saint-Constant, QC, Canada), weighing between 225 and 250 g, were studied. Pregnant rats were obtained as detailed previously (4). Age-matched NP females (selected randomly during the estrous cycle) were also investigated. The animals (6–10/group) were housed under conditions of controlled lighting (6:00 A.M. to 6:00 P.M.) and temperature (21 ± 3°C). They were fed a normal diet containing 0.23% NaCl (Teklad global 18% protein rodent diet; Harlan Teklad, Montréal, QC, Canada). Pregnant and NP animals were randomly assigned to groups that were placed either on tap water or on potassium canrenoate (C) solution (20 mg·kg⁻¹·day⁻¹; Sigma, St. Louis, MO). The beverage was given from day 15 of gestation (partition on day 23) until death or for 7 days in the NP groups. At the end of treatment, the two NP groups (untreated: NPC and the six pregnant (P) groups of rats at days 17 (P17, PC17), 19 (P19, PC19), or 22 (P22, PC22) of gestation were killed by decapitation (9:00–9:30 A.M.), and their aorta were removed for in vitro assays.

Organ bath assays. Vascular reactivity was measured, as described previously (3, 9), in thoracic aortic rings of both untreated and canrenoate-treated NPC and the six pregnant (P) groups of rats at days 17 (P17, PC17), 19 (P19), and 22 (P22) of gestation. After death, the thoracic aorta was removed rapidly, immersed in cold Krebs-bicarbonate solution (KBS), cleaned of fat and extraneous tissues, and cut into four consecutive rings (2–3 mm). The endothelium of each ring was removed by gently rubbing the lumen with an 18-gauge needle to measure changes of myotropic responses at the level of the smooth muscle. Indeed, as the vascular endothelium influences reactivity of the underlying smooth muscle (via nitric oxide, endothelial-derived hyperpolarizing factor, etc.) by activating coupling mechanisms similar to the ones used by the agonists on smooth muscle (for instance, the ion channels herein studied), we chose to remove it to get a precise picture of the consequences on the VSM. The rings were mounted in individually jacketed tissue baths (15 ml; Radnotti Glass, Monrovia, CA), maintained at 37°C, and equilibrated for 1 h under 2.0 g passive tension with frequent washing and tension adjustment. The tissues were bathed in KBS of the following composition (in mmol/l): 118 NaCl, 4.65 KCl, 25 NaHCO₃, 2.5 CaCl₂, 1.18 KH₂PO₄, 1.18 MgSO₄, and 5.5 dextrose. NaCl and MgSO₄ were purchased from Sigma Aldrich (Oakville, ON, Canada), KCl, KH₂PO₄, and NaHCO₃ from Fisher Scientific (Ottawa, ON, Canada), dextrose from J. T. Baker Chemicals (Phillipsburg, NJ), and CaCl₂ from EMD Chemicals (Gibbstown, NJ). The solution was bubbled with a mixture of 95% O₂-5% CO₂; pH was 7.4. After 1 h equilibration, tissues were challenged with 1.0 μmol/l phenylephrine (PhE). At plateau response, carbachol (0.1 mmol/l) was added to confirm endothelium removal. Tension was measured by force displacement transducers and recorded on a computerized data-acquisition system (Dataq Instruments, Akron, OH).

After return to baseline (~60 min), cumulative concentration-response curves to PhE (10⁻⁹ to 10⁻⁸ mol/l) and KCl (2–100 mmol/l, as hypertonic solution) were obtained successively. The two curves were separated by frequent washings and charted 1 h after tension from the previous maneuver had returned to baseline. One of the rings from each animal served as control, whereas each of the other three was preincubated with a VDCC blocker (nifedipine, 0.1 μmol/l), a BKCa channel activator (NS-1619, 30 μmol/l), or a KATP channel activator (cromakalim, 1 μmol/l) (all from Sigma Aldrich) added 10 min before initiating the curve. The concentrations of these agents were chosen on the basis of previous work (3, 9, 35). Each ring was exposed to the same ion channel modulator throughout the experiment. All experiments were performed under sodium lamps to prevent photo inactivation of nifedipine and NS-1619.

Data analysis. Concentration-response curves were analyzed by computer fitting to a four-parameter logistic equation (Prism 4.0; GraphPad, San Diego, CA) to evaluate the maximum response (Emax) (Table 1). Sensitivity (−log of EC⁵₀, the concentration producing 50% of Emax) was not analyzed since reduction of Emax was often very important and the EC⁵₀ is artificially decreased. The effect of the ion channel modulators was determined with a one-way ANOVA followed by a Dunnett’s test vs. the control aortic rings of a same group. Statistical significance was assumed when the difference reached the probability level of 5% (P < 0.05). The effects of both pregnancy and canrenoate treatment were evaluated on Emax by two-way ANOVA. To compare the inhibitory capacity of each modulator, we calculated the difference of Emax between the curve in the presence and absence of a modulator in each group. These delta values were used to build the bar graphs in Figs. 2 and 3. Once again, two-way ANOVA was used to evaluate the effects of pregnancy and canrenoate treatment on the inhibitory action of each modulator. ANOVA, when significant, was followed by the Bonferroni posttest. Statistical significance was assumed when the difference reached the probability level of 5% (P < 0.05). The results are expressed as mean values ± SE in grams of tension. PhE, phenylephrine; −, absence; +, presence of canrenoate. *P < 0.05 vs. control aortas.

### Table 1. Maximum responses of aortic rings to PhE and KCl in absence (control) and presence of ion channels modulators (nifedipine, NS-1619, or cromakalim)

<table>
<thead>
<tr>
<th>Modulator</th>
<th>Nonpregnant</th>
<th>17 Days Pregnant</th>
<th>19 Days Pregnant</th>
<th>22 Days Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>PhE</td>
<td>2.33 ± 0.12</td>
<td>2.64 ± 0.13</td>
<td>1.75 ± 0.06</td>
<td>2.00 ± 0.06</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>2.24 ± 0.13</td>
<td>2.31 ± 0.10</td>
<td>1.44 ± 0.09*</td>
<td>1.33 ± 0.08*</td>
</tr>
<tr>
<td>NS-1619</td>
<td>1.73 ± 0.14*</td>
<td>2.54 ± 0.12</td>
<td>1.27 ± 0.05</td>
<td>1.40 ± 0.11*</td>
</tr>
<tr>
<td>Cromakalim</td>
<td>2.16 ± 0.12</td>
<td>2.30 ± 0.11</td>
<td>1.00 ± 0.06*</td>
<td>0.86 ± 0.05*</td>
</tr>
<tr>
<td>KCl</td>
<td>1.84 ± 0.05</td>
<td>2.23 ± 0.06</td>
<td>1.41 ± 0.04</td>
<td>1.70 ± 0.04</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.52 ± 0.08*</td>
<td>0.63 ± 0.08*</td>
<td>0.30 ± 0.06*</td>
<td>0.32 ± 0.06*</td>
</tr>
<tr>
<td>NS-1619</td>
<td>1.07 ± 0.07*</td>
<td>1.85 ± 0.08*</td>
<td>0.79 ± 0.06*</td>
<td>0.93 ± 0.06*</td>
</tr>
<tr>
<td>Cromakalim</td>
<td>2.12 ± 0.07*</td>
<td>2.34 ± 0.08*</td>
<td>1.48 ± 0.06</td>
<td>1.48 ± 0.06*</td>
</tr>
</tbody>
</table>

Values are means ± SE in grams of tension. PhE, phenylephrine; −, absence; +, presence of canrenoate. *P < 0.05 vs. control aortas.
RESULTS

Effect of canrenoate on aortic responses to PhE and KCl. Figure 1 and Table 1 depict the results obtained with concentration-response curves to PhE and KCl. The two-way ANOVA analysis on the E_{max} shows significant impacts of both the time of gestation and canrenoate treatment on aortic responses to PhE (P < 0.001; Fig. 1A). Indeed, pregnancy induced reduction of E_{max} that was already evident at day 17 and persisted until term gestation (P < 0.001 vs. NP; Fig. 1A). Canrenoate, on the other hand, significantly increased responses to PhE in all groups (P < 0.001, 2-way ANOVA) although the Bonferroni test gave significance for P22 only (P < 0.05 vs. NP; Fig. 1A).

E_{max} to KCl was significantly decreased by gestation and significantly increased by canrenoate treatment (both P < 0.001, 2-way ANOVA; Fig. 1B). The reduced KCl responses of the aortas were already present at day 17 and persisted until term (P < 0.001 vs. NP; Fig. 1B). With the Bonferroni test, the increase of E_{max} by canrenoate was only significant for NPC and PC17 (both P < 0.001 vs. NP and P17, respectively; Fig. 2A). This is also shown in the first line of the two sections of Table 1 (control).

Effect of canrenoate on aortic responses to PhE, influence of ion channel modulators. The potassium channel activators NS-1619 and cromakalim attenuated aortic PhE responses (Table 1). In NP rats, this was only significantly observed in...
untreated animals with NS-1619, but it is significantly present in all groups of pregnant animals for both potassium channel activators (Table 1). Figure 2A clearly illustrates an opposite effect between time of gestation and canrenoate treatment on the ability of NS-1619 to reduce PhE responses. This is illustrated by significant interaction in the two-way ANOVA ($P < 0.001$). As term of pregnancy approached, the capacity of NS-1619 to interfere with PhE responses was reduced, an outcome that was the inverse with canrenoate treatment. On the other hand, pregnancy significantly increased the efficacy of cromakalim to lower the $E_{\text{max}}$ of PhE ($P < 0.001$, 2-way ANOVA; Fig. 2B). Furthermore, canrenoate treatment further increased cromakalim’s inhibitory effect on PhE responses ($P < 0.001$, 2-way ANOVA), with significant elevations on days 17 and 22 (both $P < 0.05$ vs. P17 and P22, respectively; Fig. 2B).

Nifedipine also induced significant reduction of PhE responses, but only in aorta of pregnant animals (Table 1). In the untreated groups, nifedipine was only able to reduce PhE responses in the aorta of pregnant animals at day 17 and 19 (Table 1 and Fig. 2C). Again, canrenoate treatment significantly increased the attenuating effect of nifedipine (as for potassium channel activators) on $E_{\text{max}}$ to PhE ($P < 0.001$, 2-way ANOVA; Fig. 2C).

**Effect of canrenoate on aortic responses to KCl, influence of ion channel modulators.** Cromakalim and NS-1619 had very different outcomes on KCl contraction curves. Cromakalim was a weak inhibitor of KCl and even increased $E_{\text{max}}$ to KCl in some groups (Table 1 and Fig. 3B). NS-1619, on the other hand, markedly lowered $E_{\text{max}}$ in all groups (Table 1 and Fig. 3A). As for the response to PhE, pregnancy and canrenoate treatment had opposite effects on NS-1619’s action (interaction $P < 0.001$, 2-way ANOVA; Fig. 3A). Indeed, inhibition by NS-1619 was lowered as pregnancy progressed to term ($P < 0.01$ for P19 and P22 vs. NP; Fig. 3A), whereas canrenoate decreased the inhibitory effect of NS-1619 on NPC ($P < 0.01$ vs. NP; Fig. 3A) and reinforced it in the aorta of pregnant rats ($P < 0.01$ for PC22 vs. P22; Fig. 3A).

Nifedipine (0.1 μmol/l) is a very efficient inhibitor of KCl responses. It markedly lowered $E_{\text{max}}$ in all groups compared with aortas in the absence of modulators (Table 1). Furthermore, its effect was diminished by the progression of pregnancy ($P < 0.001$, 2-way ANOVA; Fig. 3C), demonstrated by significant differences in the P19 and P22 groups (both $P < 0.01$ vs. NP; Fig. 3C). In contrast, canrenoate treatment augmented nifedipine’s inhibitory power ($P < 0.001$, 2-way ANOVA; Fig. 3C).

**DISCUSSION**

The present study was undertaken to determine if MR antagonism influences the development of blunted responses to vasoconstrictors accompanying pregnancy. We evaluated the impact of canrenoate treatment of pregnant rats on PhE- and KCl-induced aortic contractions and on the involvement of calcium and potassium channels, via their pharmacological modulation, in these contractions. We first demonstrated that the responses to PhE and KCl were decreased in the aortic rings of pregnant rats (Fig. 1, A and B), confirming earlier observations on blunted responses to vasopressors associated with gestation (3, 9, 24, 30, 33, 34, 38). Interestingly, these blunted responses were already evident at P17, before the BP reduction that usually occurs at P18 (4). This implies that reduced reactivity to vasoconstrictors could be involved in decreased peripheral resistance responsible for the drop in BP. This fits with Chapman et al. (10) who demonstrated peripheral vasodilatation very early in human pregnancy, before full placentation and in linkage with RAA system activation. As suggested elsewhere (36), it is suspected that generalized vasodilatation is the consequence of some hormonal stimulus linked to RAA system activation that evokes gradual increases of plasma volume and cardiac output to maintain BP. By the
end of the first trimester, when these compensatory mechanisms are not sufficient anymore, BP starts to drop while vascular dilatation keeps building up.

Moreover, treatment with canrenoate increased the vascular responses of endothelium-denuded aortas to PhE and KCl (Fig. 1, A and B). There are discrepancies concerning signaling mechanisms for aldosterone on vascular reactivity. Heylen et al. (20) reported that, in mesenteric arteries, aldosterone-induced vasodilation is mediated through MR but resulted in a dual action, endothelium-dependent dilation and smooth muscle-dependent constriction. Furthermore, MR can be activated by both aldosterone and corticosterone, but the presence of 11β-hydroxysteroid dehydrogenase-2 in VSMC and endothelial cells, converting the latter in inactive cortisone, makes the vasculature more responsive to aldosterone than corticosterone through MR. In the present study, corticosterone levels varied within untreated pregnant groups while no difference was noted between the canrenoate-treated animals (data not shown). However, it is impossible to assess here the impact of corticosterone on the vascular effects of canrenoate treatment in pregnant animals. Recent experiments have shown that aldosterone could act directly on VSM by nongenomic and genomic mechanisms (8, 17, 43), with regulation of ion handling by VSMC being frequently reported. Because ion channels are major partners in the control of vascular reactivity, it could explain how our in vivo treatment modified the vascular responses.

Modulation of ion channel activity. Several studies reported involvement of ion channels in the control of vascular reactivity during pregnancy (3, 9, 14, 22, 33, 34). In agreement with previous reports (3, 9), we have observed that PhE responses were greatly reduced by activators of KATP (cromakalim, 1 μmol/l) and BKCa (NS-1619, 30 μmol/l) while the latter and VDCC inhibitor (nifedipine, 0.1 μmol/l) were more efficient in inhibiting KCl responses.

In the present experiments, cromakalim exerted an enhanced inhibitory effect on PhE-induced contractions in the aortas of pregnant groups compared with NP ones (Fig. 2B). The inhibitory action of cromakalim is believed to be due to increased probability of the open state of KATP channels (6). The ATP-to-ADP ratio controls basal KATP activity in VSMC (15, 16, 29), and we suggest that in pregnancy the ratio could be decreased, resetting basal KATP activity. It has been shown that KATP channel activity is increased in VSMC during pregnancy (3, 9, 22), which could be attributed to metabolic changes (19). Moreover, it has been reported that in metabolically inhibited states, such as hypoxia or ischemia, a fall in the intracellular ATP-to-ADP ratio will activate KATP currents favoring vasodilatation (for review, see Ref. 16). Our results, together with the above considerations, are suggestive of an involvement of MR in this control of KATP activity in gestation. Indeed, treatment with canrenoate further increased the inhibitory effect of cromakalim in the pregnant groups (Fig. 2B). Further analyses will be necessary to investigate the signaling mechanisms involved in this regulation.

In contrast, our results with NS-1619 show decreased inhibitory effects of the BKCa activator on PhE and KCl contractions as we get closer to term (Figs. 2A and 3A), indicating different degrees of involvement for both BKCa and KATP in the control of VSMC responses during pregnancy. As previously reported (3, 9), KATP seems to be more involved in the control of resting membrane potential, by either induced hyperpolarization or retarded development of myotropic responses. On the other hand, it appears that BKCa activation prevents the full expression of myotropic responses, as suggested by Nelson et al. (27). Because BKCa are primarily regulated by voltage and intracellular calcium (21), pregnancy could control their activity by influencing the frequency of calcium sparks and membrane potential. However, because their activity is also determined by phosphorylation and by small molecules, such as steroids, fatty acids, phosphatidylinositol 4,5-bisphosphate, and reactive oxygen species (21), different signaling pathways could alter BKCa activity during pregnancy. For example, it has been reported that estrogens can relax arteries through activation of BKCa (12, 41, 44), and that, during pregnancy, an altered expression of BKCa subunits contributed to estrogen-mediated increases in ovine uterine blood flow (31, 32). However, in rat aorta, estrogens’ treatment did not modify BKCa expression, suggesting some tissue-selective influence of estrogens on the potassium channel expression (40). Aldosterone can also affect BKCa activity, since its overexpression in mice altered VSMC BKCa expression and coronary BKCa-dependent relaxation (1).

Our results clearly revealed some role of the MR in the regulation of BKCa activity. In the groups treated with canrenoate, inhibition by NS-1619 was reduced in the aortas of NP rats, whereas it was increased in pregnant rats (Figs. 2A and 3A). It is not known if the modulation of BKCa activity during pregnancy is the result of an altered expression of its subunits, a change in the stoichiometric composition, or a direct effect of aldosterone that would modulate the gating properties of the channel. This is presently under study.

In untreated pregnant animals, the inhibitory effects of nifedipine on KCl were less potent than in NP rats (Fig. 3C). This is consistent with the observation that the blunted responses to vasoconstrictors of pregnancy could be due to some functional VDCC alterations (11, 34). Indeed, Roy et al. (34) showed that extracellular calcium mobilization of aortic ring, through VDCC, was delayed at the end of pregnancy. Here, we report that the reduction of nifedipine’s effect gradually appeared as the rats come closer to the end of gestation, indicating that the open probability of VDCC varies during pregnancy to adapt or participate in hemodynamic changes. It is well-documented that the open probability of VDCC is mostly influenced by membrane potential (28), and this correlates the increased BKCa activity described above with the observed decrease in VDCC activity. Moreover, nifedipine’s inhibitory effect is enhanced in the group receiving canrenoate treatment (Fig. 3C), suggesting increased VDCC activity. It is possible that mineralocorticoids impact calcium channels by nongenomic mechanisms either directly or through phospholipase C and protein kinase C (43). Mironneau (25) demonstrated that spironolactone inhibits slow calcium channels of VSMC in a manner similar to that of calcium channel blockers. By analogy, it is possible that canrenoate could act in a similar way since both compounds share the same metabolite, canrenone. The increased inhibitory effect of nifedipine, observed in all groups, could then be an additive effect of channel inhibition by canrenoate. However, our results are consistent with what was noted when the animals received a high-sodium diet (3) that suppressed the RAA system, reinforcing our belief that MR are implicated in the regulation of VDCC activity.

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In summary, the present study supports our hypothesis that mineralocorticoids participate in the blunted responses to vasoconstrictors associated with pregnancy. Furthermore, our results demonstrated the involvement of VDCC, K\textsubscript{ATP}, and BK\textsubscript{Ca} in the regulation of vascular reactivity and indicate significant regulation of these channels by mineralocorticoids. While these data are indirect measurements of ion channel activity, this study is, to our knowledge, the first to functionally evaluate the involvement of MR in the blunted vascular responses associated with normal pregnancy. Studies are needed to characterize the signaling pathways of mineralocorticoid actions in VSMC during pregnancy. Furthermore, the role of endothelium will need to be assessed to get a full representation of the MR regulation in vivo. The involvement of MR in the control of vascular reactivity as pregnancy gets closer to term could help support the hemodynamic changes that occur simultaneously. Moreover, understanding how they impact vascular reactivity can provide insights in pathologies like preeclampsia, where the RAA system is less activated (36).

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DISCLOSURES

No conflicts of interest are declared by the authors.

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