Increased Na\textsuperscript{+} intake during gestation in rats is associated with enhanced vascular reactivity and alterations of K\textsuperscript{+} and Ca\textsuperscript{2+} function

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During normal pregnancy in rats, plasma volume and cardiac output are increased, whereas peripheral resistance and arterial blood pressure are decreased (23). These hemodynamic alterations have been linked to diminished constriction of blood vessels, thereby reducing peripheral resistance (31). However, the physiological influences that mediate the decrease in blood pressure remain unknown. Pregnancy-associated blunted responses to vasoconstrictors has been observed in isolated blood vessels of pregnant rats in the presence and absence of endothelium (15, 23, 24), indicating that they are not a consequence of autonomous reflex (7, 15), not linked to downregulation of vasoconstrictor receptors (22), or to increased endogenous vasodilator release (33). This resistance of isolated arteries of pregnant animals to vasopressors is thought to be the result of decreased myotropic influence on arterial vessels, through uncoupling of receptor-response to contractile stimuli (21, 31).

Voltage-dependent calcium channel (VDCC) antagonists are less potent in inhibiting vascular smooth muscle responses to vasoconstrictors during pregnancy (24, 25, 32). It has been observed that gestation is characterized by diminished calcium influx in isolated aorta, suggesting that mechanisms utilizing calcium for vascular smooth muscle contraction could be altered. The function of VDCC, especially L-type calcium channels, seems to be changed because of some membrane potential modification during pregnancy. It has been reported (16) that smooth muscle cells from mesenteric resistance arteries of pregnant rats are hyperpolarized by 7 mV. Recent work from our laboratory supports this observation. Indeed, we have demonstrated that tetraethylammonium (TEA), a nonselective K\textsuperscript{+} channel inhibitor, evoked contractile responses of the thoracic aorta of nonpregnant rats but not of pregnant animals. Responses were restored in the later group on preincubation in low KCl concentration (4, 24). High-conductance Ca\textsuperscript{2+}-activated potassium channels (BKCa) have been shown to be activated during gestation, decreasing responses to phenylephrine (PE), arginine vasopressin (AVP), and KCl. Activation of K\textsubscript{ATP} appeared to be involved in the regulation of resting membrane potential, reported to be increased during pregnancy (16). Such hyperpolarization could result in delayed opening of VDCCs and, consequently, retarded contraction (4). However, activation of calcium channels, induced by treating pregnant rats with a calcium channel activator, CGP-28392 (10 mg·kg\textsuperscript{-1}·day\textsuperscript{-1}), did not reverse the decline of blood pressure of pregnant animals. Moreover, CGP-28392 did not modify the reduced influence of the VDCC modulators, nifedipine and BAY K 8644, on the responses of aortic rings to KCl (29).

Recently, we have reported that supplementing the diet of pregnant rats (end of pregnancy) with 0.9% NaCl or 1.8% NaCl as drinking water resulted in inhibition of the renin-angiotensin-aldosterone system (RAAS), but most importantly, it obliterated the decrease in arterial blood pressure of the end of gestation (0.9% NaCl supplementation) or induced blood pressure increase over the prepregnant level (1.8% NaCl sup-
plementation) (3). To document the consequences of increased sodium intake on vascular reactivity, we investigated the responses of the thoracic aorta of these rats to several vasoconstrictors as well as the modulation of these responses by calcium channel inhibition and potassium channel activation, as reported previously (4, 24). We postulated that NaCl-supplemented diets, in addition to preventing the end gestational decrease in blood pressure and reducing RAAS (3), will reverse the pregnancy-associated blunting of vasoconstrictor effects that are normally seen during this period of gestation in rats.

**MATERIALS AND METHODS**

**Animals.** Female Sprague-Dawley rats (Charles River Canada, St-Constant, Québec) weighing 225–250 g and aged 10–11 wk were mated with males. The morning when spermatozoa were found in vaginal smears was deemed to be day 1 of pregnancy. Age-matched nonpregnant rats served as controls and were picked randomly during the estrous cycle. All animals were housed under controlled lighting (from 6 AM to 6 PM) and temperature (21°C ± 3°C) and received normal diet (Charles River rodent chow no. 5075). The study protocol was approved by the institutional animal care committee accredited by the Canadian Council on Animal Care.

**Treatment protocol.** Rats were divided into six groups: nonpregnant and pregnant controls that received tap water and nonpregnant and pregnant experimental animals that were given 0.9% NaCl or 1.8% NaCl as drinking water. The treatments lasted 7 days, from day 15 to 22 of experimentation, which corresponds to the last week of 3-wk gestation. As reported previously (3), such maneuver results in important sodium intake that was equivalent, for each supplement, in nonpregnant and pregnant animals.

**Organ bath assay.** Vascular reactivity was measured in thoracic aorta rings as described previously (4, 24, 33). After decapitation, the thoracic aorta was removed rapidly, cleaned of fat and extraneous tissues, and cut into four consecutive rings (2–3 mm). The endothelium of each ring was gently removed by rubbing the lumen with a 18-gauge needle. The rings were mounted in individual jacketed tissue baths (15 ml; Radnotti Glass; Monrovia, CA) maintained at 37°C and equilibrated for 60 min under 2.0 g passive tension with frequent washing and tension adjustment (4, 24, 25). The tissues were bathed in Krebs bicarbonate solution (KBS) of the following composition (in mmol/l): 118 NaCl, 4.65 KCl, 25 NaHCO3, 2.5 CaCl2, 1.18 MgSO4, 1.18 KH2PO4, and 5.5 dextrose. The solution was bubbled with a mixture of 95% O2–5% CO2; pH was 7.4. After 60 min equilibration, the tissues were challenged with 1.0 μmol/l PE. At plateau response, the tissues were washed and performed 1 h after tension from previous maneuver had returned to baseline. In each experiment, aortic rings from both nonpregnant and pregnant rats were assayed simultaneously. One of the rings from both nonpregnant and pregnant groups (under the same sodium intake) served as the control, whereas each of the other rings was preincubated with nifedipine (0.1 μmol/l), cromakalim (1 μmol/l), or NS-1610 (10 μmol/l) added 10 min before charting the curve. Concentrations of these agents were derived from previous work (4, 24). Each ring was exposed to the same inhibitor or activator throughout the experiment.

**Data analysis.** Each concentration-response curve was analyzed by computer fitting to a four-parameter logistic equation with the Prism 3.0 program (GraphPad Software, San Diego, CA) to evaluate the concentration producing EC50, and the maximum asymptote of the curve (Emax). Different curves from the same protocol were compared with one-way ANOVA of mean pD2, the negative logarithm of the concentration producing EC50, and of mean Emax using the statistical package of the Prism program. Statistical significance was obtained when P < 0.05. Data are expressed as means ± SE experimental points along the best curve fitted to these points. In the figure legends, n is number of aortic rings, all coming from different animals.

**Drugs and chemicals.** All salts used in these experiments were of analytical grade and obtained from Fisher Scientific (Montréal, Canada). PE hydrochloride, carbamylcholine chloride (carbachol), TEA chloride, and cromakalim were purchased from Sigma (St. Louis, MO). Nifedipine hydrochloride and NS-1619 were obtained from Research Biochemical International (Natick, MA). AVP was purchased from Peninsula Laboratories (Belmont, CA). Cromakalim was prepared in 70% ethanol, and NS-1619, in DMSO.

**RESULTS**

**Effects of pregnancy and sodium supplementation on TEA responses.** Responses to TEA (Fig. 1) were obtained in aortic rings of nonpregnant (solid circles) but not in pregnant (solid squares) rats on the normal diet (Fig. 1A) and sodium supplemented (0.9%, Fig. 1B, and 1.8%, Fig. 1C) diets. In the aorta of nonpregnant rats on 1.8% NaCl, the maximal response to TEA was decreased, compared with the two other nonpregnant groups.
groups. Sensitivity to TEA in rings from nonpregnant rats was not significantly altered with sodium supplements.

As shown previously (4), when tissues were precontracted with 10 mmol/l KCl, responses to TEA were observed in rings of all pregnant animals (Fig. 1, open squares). The maximal response to TEA was unchanged in the aorta of all nonpregnant groups (Fig. 1, open circles), but the concentration-response curves were markedly left shifted, indicating increased sensitivity to the K+-channel blocker. In tissues from pregnant animals, responses to TEA in the presence of KCl were always weaker than in the corresponding nonpregnant rats, except with PE in nonpregnant but not in pregnant rats (Fig. 2A). Reactivity to KCl was significantly reduced in aortic rings from nonpregnant animals (from 2.29 ± 0.07 to 1.82 ± 0.05 g, P < 0.01; Fig. 2A, left and middle) but not during NaCl supplementation (Fig. 2, B and C). Increased sodium intake did not affect sensitivity of the aorta to PE in all conditions. NaCl (1.8%) was associated with reduction of the maximum response to PE in aortic rings from nonpregnant animals (from 2.29 ± 0.07 to 2.01 ± 0.06 g; P < 0.05). In contrast, both NaCl supplements were associated with increased maximum the response to PE in pregnant rats (Fig. 2, right). 2.15 ± 0.08 and 1.92 ± 0.05 g, respectively.

Nifedipine significantly reduced the maximum response to PE under all conditions. On normal sodium intake, it diminished $E_{\text{max}}$ significantly more in the aortas of nonpregnant than pregnant rats (Fig. 2A). With sodium supplementation (0.9% and 1.8% NaCl), the reduced inhibitory effect of nifedipine in pregnant rats was no longer present (Fig. 2, B and C, right). Nifedipine significantly decreased sensitivity of the aorta from nonpregnant rats to PE but not that of pregnant animals. Cromakalim was very efficient in reducing maximum response to PE. This reduction was smaller in the aortic rings of pregnant than of nonpregnant animals, but it was much increased in the aorta of pregnant rats on both sodium supplements (Fig. 2, right). Cromakalim significantly lowered aortic rings sensitivity to PE, but this effect was not influenced by gestation and sodium supplements. NS-1619 decreased $E_{\text{max}}$ to PE in nonpregnant but not in pregnant rats (Fig. 2A). This difference was abolished (0.9%) or reversed (1.8%) by NaCl supplements (Fig. 2, B and C, right).

These results show that all three modulators decreased the maximum response to PE more importantly in the aorta from nonpregnant than pregnant rats on normal sodium intake only, but this difference was not present, or was much reduced, on sodium supplements. Aortic rings responded to PE similarly in nonpregnant and pregnant rats given 0.9% and 1.8% NaCl.

Effects of pregnancy and sodium supplementation on KCl responses. Reactivity to KCl was significantly lowered in aortic rings from pregnant compared with nonpregnant rats on normal sodium intake (from 1.72 ± 0.06 to 1.45 ± 0.05 g, P < 0.05; Fig. 3A). This difference was not maintained in animals on both sodium supplements (Fig. 3, B and C, right). Indeed, responses to KCl increased in the aorta of pregnant rats under the two sodium supplements. This resulted in identical $E_{\text{max}}$ for KCl in the aorta of nonpregnant and pregnant animals under both sodium supplements and of nonpregnant rats on regular diet (Fig. 3, right, *o* symbols). Sodium supplements had no effect on sensitivity to KCl, except a reduction in pregnant rats under 1.8% NaCl.

Nifedipine induced greater inhibition of KCl than of PE responses (Fig. 3, right). It reduced both sensitivity and $E_{\text{max}}$ of aortic rings to KCl under all sodium intakes. This inhibitory effect was significantly more pronounced in the aorta of nonpregnant than of pregnant animals; e.g., it was not obliterated under sodium supplementation as for PE. Cromakalim significantly reduced $E_{\text{max}}$ of KCl in the aorta of both nonpregnant and pregnant rats (Fig. 3, right). This effect was significantly larger in aorta of nonpregnant than pregnant animals on the normal diet and on 1.8% NaCl (Fig. 3, right). Cromakalim markedly decreased sensitivity to KCl in all groups of aorta. This is illustrated in Fig. 3 by significant rightward shifts of the concentration-response curves to KCl, except in pregnant rats on 1.8% NaCl. NS-1619 significantly lowered the $E_{\text{max}}$ of aortic rings to KCl in both nonpregnant and pregnant rats (Fig. 3, right). It significantly diminished sensitivity to KCl to similar levels under all conditions, except in pregnant rats on 1.8% sodium supplementation.

These data reveal that the aortic responses to KCl were diminished during pregnancy with normal but not with increased NaCl intake. Nifedipine induced by far the largest diminution of reactivity to KCl that was lower in pregnant than in nonpregnant rats on all salt intakes. Cromakalim and NS-1619 caused small reductions of $E_{\text{max}}$ to KCl that was more important in nonpregnant than in pregnant rats on the normal diet but not under NaCl supplements.

Effects of pregnancy and sodium supplementation on AVP responses. Gestation caused marked reductions in both $E_{\text{max}}$ (from 2.46 ± 0.09 to 1.74 ± 0.07 g, P < 0.01; Fig. 4A) and sensitivity to AVP that were not observed when the rats were supplied with 0.9% or 1.8% NaCl (Fig. 4, B and C). Both sodium supplements decreased $E_{\text{max}}$ to AVP in aortic rings of nonpregnant rats while increasing $E_{\text{max}}$ in rings of pregnant animals. Sensitivity to AVP was reduced by 1.8% NaCl in nonpregnant, but not in the pregnant animals.

Nifedipine decreased the $E_{\text{max}}$ to AVP under all conditions (Fig. 4C). It produced a significantly larger $E_{\text{max}}$ reduction in the aorta of nonpregnant than pregnant rats (Fig. 4A) but not on sodium supplements (Fig. 4, B and C). Nifedipine did not influence sensitivity to AVP. Cromakalim reduced $E_{\text{max}}$ more importantly in nonpregnant than in pregnant rats (Fig. 4A). The inhibitory effect of cromakalim on AVP responses was similar in nonpregnant and pregnant animals on 0.9% and 1.8% NaCl (Fig. 4, B and C). It is noteworthy that the K ATP activator reduced sensitivity to AVP in only all nonpregnant groups. NS-1619 importantly lowered the $E_{\text{max}}$ to AVP in the aorta of pregnant rats on 0.9% NaCl (Fig. 4B). NS-1619 did not alter sensitivity to AVP.

These results demonstrate that, on 0.9% and 1.8% NaCl supplementation, aortic ring responses to AVP were very similar in nonpregnant and pregnant animals. The reduced inhibitory effects of nifedipine and cromakalim in the aortic
Fig. 2. Concentration-response curves to phenylephrine (PE) in aortic rings from nonpregnant (left) and pregnant (middle) rats on either normal (A) or increased sodium intake with 0.9% (B) or 1.8% NaCl (C) supplements. Curves were obtained in the absence (control) and presence of (in µmol/l) 0.1 nifedipine, 1 cromakalim, or 10 NS-1619. Each curve is the best fit to means ± SE experimental points, obtained in 10 aortic rings from different animals. Paired columns (aortas of nonpregnant and pregnant animals) show differences in maximum response of the curve ($E_{\text{max}}$) to PE relative, for controls (Co$^\circ$), to nonpregnant animals on normal diet, or, for nifedipine (Nif$^\circ$), cromakalim (Cro$^\circ$), and NS-1619 (NS$^\circ$)-treated aortas, to corresponding nonpregnant or pregnant animals on same sodium intake. ∗∗, Data not different from null value. *$P < 0.05$, statistical significance between aorta of nonpregnant and pregnant rats on the same treatment.
Fig. 3. Concentration-response curves to KCl in aortic rings from nonpregnant and pregnant rats on either normal (A) or increased sodium intake with 0.9% (B) or 1.8% NaCl (C) supplements. Curves were obtained in the absence and presence of (in μmol/l) 0.1 nifedipine, 1 cromakalim, or 10 NS-1619. Each curve is the best fit to means ± SE experimental points, obtained in 10 aortic rings from different animals. Paired columns (aortas of nonpregnant and pregnant animals) at right are $E_{\text{max}}$ to KCl relative, for controls, to nonpregnant animals on normal diet or, for nifedipine-, cromakalim-, and NS-1619-treated aortas, to corresponding nonpregnant or pregnant animals on same sodium intake. α, Data not different from null value. * $P < 0.05$, statistical significance between aortas of nonpregnant and pregnant rats on the same treatment.
Fig. 4. Concentration-response curves to arginine vasopressin (AVP) in aortic rings from nonpregnant and pregnant rats on either normal (A) or increased sodium intake with 0.9% (B) or 1.8% NaCl (C) supplements. Curves were obtained in the absence and presence of (in μmol/L) 0.1 nifedipine, 1 cromakalim, or 10 NS-1619. Each curve is the best fit to means ± SE experimental points, obtained in 10 aortic rings from different animals. Paired columns (aorta of nonpregnant and pregnant animals) in the right panels are $E_{\text{max}}$ to AVP relative, for controls, to nonpregnant animals on normal diet, or, for nifedipine-, cromakalim-, and NS-1619-treated aortas, to corresponding nonpregnant or pregnant animals on same sodium intake. * Data not different from null value. $^*P < 0.05$, statistical significance between aorta of nonpregnant and pregnant rats on the same treatment.
rings of pregnant compared with nonpregnant controls were not observed on both high-sodium diets.

**DISCUSSION**

This study was undertaken to evaluate the effects of sodium supplementation of a normal diet during pregnancy on reactivity to vasopressor agents. As we have previously reported altered influence, during gestation, of Ca\(^{2+}\) and K\(^+\) channels on responses to vasopressors, we measured the impacts of their modulation on reactivity in nonpregnant and pregnant sodium loaded rats. We confirmed our previous finding (4) of the absence of a response to TEA in aortic rings of pregnant rats, but this was maintained after sodium loading. We have also shown that sodium supplements obliterated the decreased reactivity to PE, KCl, and AVP associated with normal pregnancy. Similarly, the lower inhibitory effects of nifedipine and cromakalim on PE and AVP in aortic rings of pregnant rats were no longer present after sodium supplementation, but were maintained for nifedipine on KCl responses. NS-1619 exerted a mild inhibitory action on responses to PE that was decreased only in the aortas of pregnant rats on normal sodium intake. Under sodium supplements, NS-1619 tended to produce greater inhibition of the responses to agonists in the aorta of pregnant rats (significant for AVP at 0.9% NaCl and for PE with 1.8% NaCl). These results show that functional alterations of vascular responses to vasopressors in normal pregnancy are reverted in salt-loaded pregnant rats and support earlier observations (3) that sodium supplements in pregnant rats induce vascular manifestations that are seen in gestational hypertension (preeclampsia).

**Vascular reactivity.** It is well documented that pregnancy is associated with blunted reactivity to vasopressor agents (4, 6, 7, 15, 16, 21, 23–25, 31). This is also true in the present investigation, where it was noted for TEA, PE, AVP, and KCl. For TEA, the decreased reactivity of aortic rings from pregnant rats is virtually an all-or-none phenomenon, as shown previously (4), that can be overcome by preincubation of aortic rings with a low concentration (10 mmol/l) of depolarizing KCl. These results, combined with those reported previously for the effects of TEA (4) and of BAY K 8644 (24), support the observation of Meyer et al. (16) of hyperpolarization in smooth muscle cells of rat mesenteric resistance arteries during gestation. This also fits with the results of Storm and Webb (34) showing increased effects of BAY K 8644 in the aortas of hypertensive rats, the opposite model to pregnancy, in which blood pressure decreases (30).

In the present experiments, the different responses to TEA in the aorta of nonpregnant and pregnant rats were maintained after sodium loading (Fig. 1); e.g., there were almost no responses in pregnant rats. As reported previously (3), pregnant rats on the 0.9% NaCl supplement did not experience decreased blood pressure at the end of gestation. Moreover, those that were given 1.8% NaCl presented blood pressure elevation. We expected, as reported by Rusch et al. (26), that the responses to TEA would to be normalized to values of nonpregnant animals by a mechanisms similar to that preventing the decrease in blood pressure. Indeed, these authors noted increased effects of TEA in aortic segments of spontaneously hypertensive (SHR) and aorta-coarcted rats, effects that were linked to hypertension, at least in the latter model. They also provided evidence linking the increased response to TEA in hypertensive rats to augmented density of Maxi K (BK\(_{Ca}\)) current (28). If, as we argued previously (4), the absence of response to TEA in aorta of pregnant rats is the consequence of decreased BK\(_{Ca}\) channel density, our present results indicate that this phenomenon was not reset to the nonpregnant level by high-sodium intake in pregnant rats, although blood pressure was increased.

Vascular responses to PE, AVP, and KCl were also decreased in the aortas of pregnant compared with nonpregnant rats. However, this difference did not persist in aortic rings from pregnant rats on high-sodium intake. On the other hand, the responses to both PE and AVP increased during pregnancy with sodium loading, whereas it decreased in nonpregnant rats. The response to KCl increased in pregnant rats on sodium loading. This suggests that sodium loading affected, during pregnancy, some mechanisms in aortic smooth muscle that are important for receptor-coupled vasoconstriction but not for depolarization-induced responses. Our results with TEA support this interpretation, because responses to TEA, linked to inhibition of K\(^+\) channels, were not altered by sodium loading. A similar enhancement of PE responses was seen in salt-loaded (chow containing 8% NaCl) rats, either virgin, pregnant, or with reduced uterine perfusion pressure (2). Indeed, they found that these pregnant rats had significantly higher blood pressure and enhanced aortic reactivity to PE than pregnant rats on regular 1% NaCl diet. Their results are not easily comparable to ours, but, in endothelium-denuded aorta, it appears that the effects of PE were decreased during pregnancy, but returned to nonpregnant levels in pregnant rats on high-salt diet, i.e., observations similar to the present ones.

This suggests that high-salt intake in pregnant rats (last of 3 wk of gestation) is accompanied by obliteration of the normal decrease in blood pressure (3) and by reversal of the “blunted responses to vasoconstrictors.” These findings are somehow similar to some manifestations reported in preeclamptic pregnancies. Indeed, during the second trimester in women who will develop preeclampsia, blood pressure (17) and sensitivity to angiotensin II (13) are not decreased. Blunting of in vitro responses to angiotensin in arteries of the omentum of pregnant women and its reversal in preeclampsia has also been reported (1). Taken together, these data strongly support the concept that the animal model described herein and previously (3) represents a valuable tool to study cardiovascular alterations of pregnancy, for instance those that are observed during the second trimester of pregnancy in women who will develop preeclampsia.

**Modulation of channel functions.** Although the involvement of ion channels in vascular smooth muscle effects of vasoconstrictors has long been recognized, their role in modulating vascular tone and myotropic reactivity in pregnancy is of recent concern (4, 9–11, 14, 24, 25). In the present study, we have shown that K\(_{ATP}\) channel activation (cromakalim, 1.0 \(\mu\)mol/l) was more effective than BK\(_{Ca}\) channel activation (NS-1619, 10 \(\mu\)mol/l) and L-type calcium channel blockade (nifedipine, 0.1 \(\mu\)mol/l) in interfering with vasoconstriction induced by agonists acting on G protein-coupled receptors, PE and AVP. In contrast, calcium channel blockade was the most efficient modulator to interfere with KCl-induced depolarization. Criddle et al. (5) proposed that levomakalim, in opposition to nifedipine, relaxes mesenteric arterioles by opening
small-conductance, glibenclamide-sensitive potassium channels but that it is relatively unable to suppress the increase in intracellular Ca\(^{2+}\) concentration induced by high-K\(^+\) solution. This interpretation is in agreement with present and earlier findings (4, 24).

In animals on the normal diet, we observed that the inhibitory effects of cromakalim and nifedipine, on responses to the three vasoconstrictors, were significantly milder in the aortas of pregnant than of nonpregnant rats. NS-1619 induced greater inhibition of PE responses in the aorta of nonpregnant than of pregnant rats, but not with KCl and AVP. When K\(^+\) channels are less responsive to pharmacological activators, it is suggested that channels molecules are activated (20). This is in agreement with previous findings (4, 24) and further supports the concept of increased activity of potassium channels, especially K\(_{ATP}\) channels, contributing to the reduced reactivity of blood vessels during gestation and, hence, to the decreased peripheral resistance and blood pressure associated with this condition (4, 14).

Our data indicate that fractions of K\(^+\) channels, which are activated during pregnancy, are diminished when rats are supplemented with saline. On sodium supplements, differences between nonpregnant and pregnant rats in the inhibitory effects of the three channel modulators did not exist anymore. In patch-clamp studies, Ohya and al. (20) reported that sensitivity and maximal responses to levcromakalim (a K\(_{ATP}\) activator) in mesenteric artery cells of SHR were reduced. This agrees with results indicating that K\(_{ATP}\) channels are deactivated in smooth muscle cells of the thoracic aorta in salt-induced hypertension (19). Moreover, it has been reported that relaxation of the inferior epigastric artery to cictelanine (a K\(_{ATP}\) activator) was more important in preeclamptic than in normal pregnant women (8). Thus the possible deactivation of K\(_{ATP}\) channels observed in our study may be a feature of hypertension and of preeclampsia. In nonpregnant rats, NS-1619 partially lost its inhibitory effect when the animals received sodium supplementation. This was particularly true with 1.8% NaCl; when tissues were stimulated with AVP, the NS-1619 action was totally abolished. In aortic rings stimulated with PE, the inhibitory effect of NS-1619 was increased. In general, sodium supplementation was associated with K\(_{Ca}\) activation. As argued above, TEA-induced contractions in arteries of SHR but not of normotensive rats (27, 28); this was suggested to be linked to heightened K\(_{Ca}\) channels activity (26), through increased opening probability of VDCC by 30% (18). The number of VDCC in the inactivated state is considered reduced during pregnancy (25). Our results indicate that equilibrium between the different states of VDCC in arterial smooth muscle during pregnancy is shifted to the inactivated state (favored by nifedipine) when the rats receive sodium supplementation.

These data disclose that sodium-supplemented pregnant rats experience reversal of the blunted responses to vasoconstrictors associated with normal pregnancy. They also show that increased sodium intake can modulate the activity of potassium and calcium channels during pregnancy. K\(_{ATP}\) channel activity is decreased, whereas K\(_{Ca}\) channels and VDCC activities are increased, by sodium supplementation. These observations, added to the previous report that these rats do not experience the usual decrease in blood pressure at the end of gestation, suggest that they manifest a syndrome that resembles, in some aspects, gestational hypertension (3). Such a model represents a valuable tool to study the physiopathology of altered hemodynamic parameters similar to those occurring in preeclampsia.

**REFERENCES**