Suppression of renal sympathetic nerve activity during portal vein infusion of hypertonic saline

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Nishida, Yasuhiro, Isao Sugimoto, Hironobu Morita, Hiroshi Murakami, Hiroshi Hosomi, and Vernon S. Bishop. Suppression of renal sympathetic nerve activity during portal vein infusion of hypertonic saline. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R97–R103, 1998.—Sodium ions absorbed from the intestine are postulated to act on the liver to reflexly suppress renal sympathetic nerve activity (RSNA), resulting in inhibition of sodium reabsorption in the kidney. To test the hypothesis that the renal sympathoinhibitory response to portal venous NaCl infusion involves an action of arginine vasopressin (AVP) at the area postrema, we examined the effects of portal venous infusion of hypertonic NaCl on RSNA before and after lesioning of the area postrema (APL) or after pretreatment with an AVP V1 receptor antagonist (AVPX). Rabbits were chronically instrumented with portal and femoral venous catheters, femoral arterial catheters, and renal nerve electrodes. Portal venous infusion of 9.0% NaCl (0.02, 0.05, 0.10, and 0.15 ml·kg−1·min−1 of 9.0% NaCl for 10 min) produced a dose-dependent suppression of RSNA (−12 ± 3, −34 ± 3, −62 ± 5, and 80 ± 2%, respectively) that was greater than that produced by femoral vein infusion of 9.0% NaCl (2 ± 3, −3 ± 2, −12 ± 4, and −33 ± 3%, respectively). The suppression of RSNA produced by portal vein infusion of 9.0% NaCl was partially reversed by pretreatment with AVPX (−9 ± 3, −20 ± 3, −41 ± 4, and −55 ± 4%, respectively) and by APL (−11 ± 2, −25 ± 2, −49 ± 3, and −59 ± 6%, respectively). There were no significant differences between the effects of AVPX and APL, and the effect of APL was not augmented by AVPX. These results indicate that the suppression of RSNA due to portal venous infusion of 9.0% NaCl involves an action of AVP via the area postrema.

sodium chloride; hepatorenal reflex; vasopressin; neurohumoral interaction; area postrema

BECAUSE SODIUM (Na+) is a major cation of the extracellular body fluid, the regulation of blood Na+ levels is an important determinant of body fluid volume. Recently, Morita et al. (17) found that portal venous infusion of hypertonic sodium chloride (NaCl) solution strongly suppresses renal sympathetic nerve activity (RSNA), resulting in increases in urinary Na+ and water excretion. Not only direct infusion of Na+ to the portal vein but also oral intake of a high-Na+ diet causes suppression of RSNA and enhances urinary output (15). This portal hypertonic NaCl-induced reflex seems to be important in the regulation of body fluid balance (16, 21). The afferent limb of this reflex mechanism is thought to be the hepatic afferent nerves (14, 17), which may terminate mainly in the nucleus of the solitary tract (19). The afferent limb of this reflex is therefore clearly neural. However, its efferent limb for suppression of RSNA has not yet been clearly elucidated.

Many researchers have reported that RSNA is influenced not only by the central nervous system but also by humoral factors (2, 6, 20, 22, 28). Plasma arginine vasopressin (AVP) is postulated to act on the area postrema to suppress RSNA independently of its effects on blood pressure (20, 28). This suggests the possibility that a neurohumoral interaction could also contribute to portal hypertonic NaCl-induced suppression of RSNA. It has already been established that an increase in portal Na+ concentration stimulates the hepatic osmoreceptor to send signals through the hepatic afferent nerves to the hypothalamus, thereby enhancing AVP release from the hypothalamus into the bloodstream and increasing plasma AVP concentration (1, 3, 29). Taken together, this evidence strongly suggests that the afferent limb of the portal hypertonic NaCl-induced reflex might involve an action of AVP at the area postrema to suppress RSNA.

The goal of the present study is to examine whether administration of an AVP antagonist or lesioning of the area postrema can restore the RSNA suppression produced by portal hypertonic NaCl infusion in conscious animals.

METHODS

Surgery. Ten New Zealand White rabbits weighing 2.30–2.80 kg (mean 2.6 ± 0.06 kg) were divided into two groups: intact rabbits and those with area postrema lesion (APL). The intact rabbits were anesthetized with a subcutaneous injection of an anesthetic mixture [43 mg of ketamine, 3.6 mg of chlorpromazine, and 8.6 mg of xylazine (Rompun)/kg body wt]. With the use of sterile surgical procedures, an upper mid-laparotomy was performed to implant a portal vein catheter for the infusion of NaCl solutions. A silicone (Silastic; Dow Corning, Midland, MI) catheter was placed in the portal vein via a branch of the mesenteric vein. After the abdominal wall was closed, other Silastic catheters were placed in the lower abdominal aorta via the left femoral artery for measurement of arterial pressure and in the lower inferior vena cava via the left femoral vein for infusion of NaCl solution or other drugs. All catheters were exteriorized and heparinized every 2 days until the experiments were completed. After recovery period of at least 2 wk, the rabbits were again anesthetized and a retroperitoneal incision was made to isolate the renal nerves for the implantation of stainless steel electrodes (Medwire). The nerve and electrodes were covered with a

†Deceased 19 February 1996.
silicone gel (Wacker silicone 604A and 604B). Ampicillin (6.0 mg/kg) was administered for 2 days after each surgery. Nalbuphine (2.0 mg/kg) was administered immediately after each surgery.

The rabbits for the APL group were anesthetized using the same procedure as for the intact rabbits. Under aseptic conditions, the area postrema was exposed via a mid-occipital incision and removal of the altantooccipital membrane (4). The structure was aspirated through a 23-gauge needle attached to a suction unit. Dexamethasone (1 mg/kg), analgesics, and antibiotics were administered after surgery. The rabbits were given at least 5 wk to recover from the APL surgery and to achieve a new equilibrated state. After the recovery period, portal venous and arterial and venous catheters were implanted using the same procedure described. Two weeks later, renal nerve electrodes were implanted as described. Antibiotics and analgesics were administered after each surgery. APLs were histologically verified following the method described previously (4) after all experiments were completed. In brief, after the rabbits were anesthetized and heparinized, the brains were perfused with normal saline followed by 10% phosphate-buffered Formalin. The brain stems were removed and put in a 10% Formalin-sucrose solution for at least 2 days. Frozen sections (40 µm) were later cut and mounted. The ablated area was estimated by microscopy. The rabbits were housed in individual cages in a room dedicated to rabbits and were handled daily.

Recordings. The rabbits were trained to become familiar with the experimental environment 1 wk before experimentation. After a recovery period of at least 2 days after the renal nerve surgery, the experiments were carried out without restraint in the conscious state. On the day of the experiment, the rabbit was placed in a basket in which the animal could turn around. The femoral arterial catheter was connected to a Statham p23Db pressure transducer for measurement of arterial blood pressure. Mean arterial pressure (MAP) was obtained using a filter with a 2-s time constant. Heart rate (HR) was determined with a Beckman cardiofrequency coupler that was triggered from the arterial pressure pulse. The renal nerve electrodes were protected with a coiled wire and were connected to the amplifier system. Raw RSNA was amplified and band-pass filtered with a Grass model P15 differential preamplifier and a Princeton Applied Research model 113 preamplifier and was displayed on a Tektronix type 422 oscilloscope. Whole nerve activity was rectified and integrated with an analog device root mean square-to-direct current converter. Mean RSNA was obtained using a filter with a 2-s time constant. Background noise was determined when nerve activity was completely suppressed by increasing arterial pressure with phenylephrine. RSNA is expressed in percent from the rectified and integrated signal by a filter with a 2-s time constant. The renal nerve electrodes were implanted on the animal 2 days after a recovery period, at the end of the 10-min NaCl infusion period, and 2 h after cessation of the infusion. NaCl solution was infused through either the femoral or portal catheter at each of the four infusion rates described in Experimental protocols. One infusion rate was performed per day, with the order of infusion rate and administration route randomized. More than 1 wk was allowed for recovery between portal and femoral venous infusions. The removed blood was replaced immediately with an equivalent volume of normal saline. Blood samples collected from the animals were immediately placed on ice. Hct was determined by the capillary method. Plasma samples were obtained after centrifugation of blood samples at 4°C for 15 min and were stored at −20°C until assayed. Plasma Na+ and K+ concentrations were determined by standard flame photometry (Nova 1; Nova Biomedical, Newton, MA). Plasma osmolality was measured by the freezing point depression method (Precision Systems).

Statistical analysis. Data are expressed as means ± SE. The values were analyzed with one-way analysis of variance for comparisons among the five NaCl doses or between intact and APL groups. Significant differences between means were detected with the Newman-Keuls multiple-comparison test. Statistical significance was achieved at P < 0.05.

RESULTS

Intact group. Baseline values of MAP, HR, and RSNA of five intact rabbits before the portal and femoral venous infusions of 9.0% NaCl are shown in Table 1. During infusion, RSNA decreased markedly, with only slight increases in MAP and HR. Portal vein infusion of 9.0% NaCl significantly suppressed RSNA in a dose-dependent manner in intact rabbits (Fig. 1). MAP (Fig. 2A) was not significantly affected by the 0.02 or 0.05 ml·kg−1·min−1 infusion but was increased by both the 0.10 and the 0.15 ml·kg−1·min−1 infusion. HR (Fig. 2B) was also not significantly affected by the 0.02 or 0.05 ml·kg−1·min−1 infusion but was increased by the 0.10 and 0.15 ml·kg−1·min−1 infusion.

To examine the effects of volume per se, normal (9%) saline was infused into the portal vein at the maximum rate (0.15 ml·kg−1·min−1) used for the hypertonic saline solution. This volume load had no significant effect on RSNA (Fig. 1), MAP, or HR (Fig. 2). These results indicate that, even at the maximum infusion rate, the volume of infusion had no effect on RSNA, MAP, or HR. Therefore, the dose-related response of RSNA, MAP, and HR to hypertonic NaCl solution was dependent on the rate of NaCl delivered rather than the volume of solution.
Table 1. Resting values of MAP, HR, and RSNA before portal or femoral venous infusion of 9.0% NaCl solution

<table>
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<tr>
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<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
<th>%RSNA</th>
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<tr>
<td><strong>Portal venous infusion</strong></td>
<td></td>
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<tr>
<td>Intact rabbits</td>
<td>5</td>
<td>66.9 ± 0.8</td>
<td>206 ± 10</td>
<td>100</td>
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<tr>
<td>Without AVPX</td>
<td></td>
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<tr>
<td>With AVPX</td>
<td></td>
<td>67.4 ± 0.9</td>
<td>214 ± 10</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>APL rabbits</td>
<td>5</td>
<td>67.0 ± 2.3</td>
<td>198 ± 4</td>
<td>100</td>
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<tr>
<td>Without AVPX</td>
<td></td>
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<tr>
<td>With AVPX</td>
<td></td>
<td>68.3 ± 1.4</td>
<td>203 ± 3</td>
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<td><strong>Femoral venous infusion</strong></td>
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<tr>
<td>Intact rabbits</td>
<td>5</td>
<td>69.4 ± 2.8</td>
<td>196 ± 5</td>
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Values are pooled means ± SE of 4 baseline values obtained before 0.02, 0.05, 0.10, and 0.15 ml·min⁻¹·kg⁻¹ infusion of 9.0% NaCl solution; baseline values were pooled because there was no significant difference among these 4 values in the 5 animals of each group. MAP, mean arterial pressure; HR, heart rate; RSNA, renal sympathetic nerve activity, expressed in percentage compared with each control level before administration of arginine vasopressin receptor V₂ antagonist (AVPX); APL, area postrema lesion.

Pretreatment with AVPX had no significant effect on the resting levels of MAP, HR, or RSNA (Table 1). Portal vein infusion of 9.0% NaCl after AVPX pretreatment significantly suppressed RSNA in a dose-dependent manner (Fig. 1). However, the suppression of RSNA in rabbits pretreated with AVPX was significantly less at each dose level in the nonpretreated rabbits. MAP (Fig. 2A) was not significantly affected by either the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion but was increased by the 0.10 and 0.15 ml·kg⁻¹·min⁻¹ infusion. Similarly, HR was not significantly altered by the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion (Fig. 2B) but was increased by the 0.10 and 0.15 ml·kg⁻¹·min⁻¹ infusion.

APL group. Previous studies have indicated that APL affects the cardiovascular system immediately after surgery in rats (25) and dogs (7) and affects the drinking behaviors and the water and Na⁺ balance for several weeks in rats (30). However, food and water intake were normalized 2 wk postlesion (13). We waited >7 wk after APL before conducting the experiments to allow the rabbits to recover from the surgery of APL and to achieve a new steady state. We measured plasma Na⁺ and K⁺ concentrations, osmolality, and Hct in two of five APL rabbits before and after the portal vein infusions of 9.0% NaCl at a rate of 0.02, 0.05, 0.10, or 0.15 ml·kg⁻¹·min⁻¹. The responses of these variables in APL rabbits were similar to those of intact rabbits.

Baseline values of MAP, HR, and RSNA before portal vein infusion of 9.0% NaCl solution in APL rabbits are shown in Table 1. There was no significant difference in any variable between intact and APL rabbits. Portal vein infusion of 9.0% NaCl significantly suppressed RSNA in a dose-dependent manner in APL rabbits; the suppression at each dose was significantly less than that in intact, nonpretreated rabbits but was not significantly different from that in intact rabbits pretreated with AVPX (Fig. 1). MAP (Fig. 2A) was not altered by the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion but was increased by the 0.10 and 0.15 ml·kg⁻¹·min⁻¹ infusion. Likewise, HR (Fig. 2B) was not significantly affected by the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion but was increased by the 0.10 and 0.15 ml·kg⁻¹·min⁻¹ infusion.

In APL rabbits, pretreatment with AVPX had no significant effect on resting values of MAP, HR, or RSNA (Table 1). In these animals, portal vein infusion of 9.0% NaCl solution significantly suppressed RSNA in a dose-dependent manner. The suppression at each dose was not significantly different from the respective value in nonpretreated APL rabbits (Fig. 3). MAP (Fig. 2A) was not significantly altered by the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion but was increased by the 0.10
or 0.15 ml·kg⁻¹·min⁻¹ infusion. HR (Fig. 2B) was not significantly affected by the 0.02 or 0.05 ml·kg⁻¹·min⁻¹ infusion but was increased by the 0.10 or 0.15 ml·kg⁻¹·min⁻¹ infusion.

Femoral vein infusions. To determine whether hypertonic NaCl-induced suppression of RSNA was due to stimulation of receptors anatomically located in the liver, 9.0% NaCl solution (0.02, 0.05, 0.10, and 0.15 ml·kg⁻¹·min⁻¹) was infused systemically through the femoral venous catheter in intact rabbits (n = 5). RSNA was suppressed only at the two highest infusion rates (0.10 and 0.15 ml·kg⁻¹·min⁻¹; Fig. 4). However, the magnitude of this suppression was significantly less than that produced by portal vein infusion of the same dose of 9.0% NaCl. MAP was not altered at a rate of 0.02 or 0.05 ml·kg⁻¹·min⁻¹ but was increased at a rate of 0.10 and 0.15 ml·kg⁻¹·min⁻¹. There were no significant differences in the magnitudes of the pressor responses between portal and femoral vein infusions (Fig. 5A). HR was not altered at a rate of 0.02 or 0.05 ml·kg⁻¹·min⁻¹ but was increased at a rate of 0.10 or 0.15 ml·kg⁻¹·min⁻¹ (Fig. 5B). Again, there was no significant difference in the increases of HR between the portal and femoral vein infusions.

Changes in Hct and plasma osmolality, Na⁺, and K⁺ levels were compared between the portal and femoral vein infusions of 9.0% NaCl solution. Both femoral and portal vein infusions of 9.0% NaCl solution decreased Hct in a similar dose-dependent manner (Fig. 6B). Plasma osmolality (Fig. 6A) was not significantly altered by either femoral or portal vein infusion at a rate of 0.02, 0.05, or 0.10 ml·kg⁻¹·min⁻¹ but was increased at a rate of 0.15 ml·kg⁻¹·min⁻¹. Plasma Na⁺ level (Fig. 6C) was not significantly altered by either femoral or portal vein infusion at a rate of 0.02 or 0.05 ml·kg⁻¹·min⁻¹ but was increased at a rate of 0.10 and 0.15 ml·kg⁻¹·min⁻¹. Likewise, plasma K⁺ level (Fig. 6D) was not significantly altered at a rate of 0.02 or 0.05 ml·kg⁻¹·min⁻¹ but decreased at a rate of 0.10 or 0.15 ml·kg⁻¹·min⁻¹. Changes in Hct plasma osmolality, Na⁺, and K⁺ elicited by hypertonic NaCl were not different between the two routes of administration.

**DISCUSSION**

In this study, we have confirmed previous findings showing that portal vein infusion of hypertonic NaCl initiates a dose-dependent suppression of RSNA. This effect is due to preferential stimulation of Na⁺-sensitive sites in the liver, because femoral venous infusion of identical doses of hypertonic NaCl produced only small decreases in RSNA, even at the highest infusion rate. The primary new finding of this study is that blockade of AVP V₁ receptors in intact rabbits attenuates this suppression, as does lesioning of the area postrema; the partial reversal of the suppression in RSNA does not differ between AVPX pretreatment and APL. The observation that AVPX pretreatment of APL animals provides no further attenuation of RSNA suppression suggests that AVP acts at the area postrema to inhibit RSNA during portal vein infusion of hypertonic saline.

Portal vein infusion of hypertonic NaCl solution stimulates both the intrahepatic and extrahepatic recep-
tors (23). The two highest doses of the portal hypertonic NaCl (0.10 or 0.15 ml·kg⁻¹·min⁻¹) increased MAP by -5 or -8 mmHg, respectively (Fig. 5A). These increases in MAP may stimulate arterial baroreceptors and reflexly suppress RSNA. Furthermore, each of the four doses of 9.0% NaCl decreased Hct (Fig. 6B), suggesting the possibility that circulating plasma volume was increased. Previously, others have shown that sinoaortic denervation plus vagotomy reverses the suppression of sympathetic nerve activity produced by portal vein infusion of a hypertonic NaCl solution (17). Accordingly, it is possible that hypertonic NaCl infusion into the portal vein could also initiate arterial and cardiopulmonary baroreflexes, which could contribute to the inhibition of RSNA (12). The activation of these extrahepatic reflexes can also be achieved by femoral vein infusion of hypertonic NaCl. As shown in Figs. 5 and 6, no significant difference was found in the responses of MAP, Hct, or plasma Na⁺, K⁺, or osmolality between the portal and femoral vein infusions at each dose of hypertonic NaCl. However, the suppression of RSNA produced by femoral infusions was substantially less than that elicited by portal vein infusions (Figs. 1 and 4). Significant suppression of RSNA also occurred at the two lowest doses of portal vein hypertonic NaCl in the absence of a pressor response, suggesting that arterial baroreceptor activation did not contribute to the inhibition of RSNA. Accordingly, this difference in RSNA suppression at each dose results from activation of the intrahepatic receptors by portal vein infusion of hypertonic NaCl. Furthermore, small increases in plasma Na⁺ concentrations in the range observed as the lowest rate of infusion (∼3.5 meq/l) has been shown to stimulate hepatic sodium-sensitive mechanisms leading to a decrease in RSNA (14, 18).

Finally, it should be mentioned that portal vein infusion of hypertonic NaCl may also increase portal or hepatic venous pressure, activating the hepatic baroreceptor (11). However, increases in hepatic venous pressure have been shown to act via the hepatic baroreceptor to reflexly increase RSNA (11). There is also evidence supporting the existence of osmoreceptors in the liver (1, 3, 29). Ishiki et al. (8) showed that stimulation of hepatic osmoreceptors with either hypertonic NaCl, LiCl, or glucose solution suppressed RSNA via the hepatic afferent nerves. Although the sensitivity of the hepatic osmoreceptors is unknown, activation of these receptors might also contribute to the suppression of RSNA shown in the present study.

As discussed, the suppression of RSNA to portal vein infusion of hypertonic NaCl is thought to be entirely due to activation of a neural reflex. However, neural reflexes can also be modulated by circulating hormones, including angiotensin II (4, 22), atrial natriuretic peptide (6), and AVP (20, 26, 28). For example, exogenous AVP dose-dependently suppresses RSNA over a wide range of blood pressures (20). Undesser et al. (28) found that lesioning the region of the area postrema abolishes the AVP-evoked suppression of RSNA. These findings suggest that RSNA may be suppressed by an action of AVP at the area postrema. The area postrema is a circumventricular organ located in the caudal medulla of the brain (13). Circulating humoral factors can have access to this site because it lacks a complete blood-brain barrier (5). Additional studies showed that circulating AVP can modulate the arterial (20) and cardiopulmonary (2) baroreflexes via an action at the area postrema (27). Thus one has to assume that part of the suppression of RSNA caused by
portal vein hypertonic NaCl infusion could result from the action of AVP on the area postrema.

In addition to activating intrahepatic Na$^+$ and/or osmoreceptors, portal vein infusion of hypertonic NaCl would also stimulate the release of AVP from the pituitary. Baertschi and Vallet (3) have demonstrated that plasma AVP increases within 1 min after portal vein infusion of hypertonic NaCl solution and that the increase in plasma AVP resulted from activation of intrahepatic osmoreceptors (29). Studies by Kobashi and Adachi (9) showed that hepatoportal osmoreceptive signals are conveyed via vagal afferents to the projections from the nucleus of the solitary tract and the caudal ventrolateral medulla and then to the paraventricular and supraoptic neurosecretory neurons (24), leading to the secretion of AVP. In the present experiments, pretreatment with AVPX partially reversed the portal vein Na$^+$-induced suppression of RSNA in intact rabbits even at the lower dose (0.05 ml·kg$^{-1}$·min$^{-1}$). At an identical dose, APL also partially reversed the RSNA suppression in an identical fashion to that obtained by pretreatment with AVPX in intact rabbits. However, pretreatment with AVPX in APL rabbits had no additional effects on RSNA (Fig. 3). These findings suggest that the mechanism of RSNA suppression by stimulation of the intrahepatic Na$^+$ receptor and/or osmoreceptor may involve an action of AVP on the area postrema.

In conclusion, the present study indicates that the intraportal infusion of hypertonic NaCl may stimulate the intrahepatic Na$^+$ and/or osmoreceptor at lower doses and also the extrahepatic Na$^+$ and/or osmoreceptor at higher doses, resulting in a suppression of RSNA greater than that observed with similar infusions administered in the femoral vein. One mechanism responsible for the suppression of RSNA occurs in response to the reflex increase in AVP and its resetting action at the area postrema.

Perspectives

Hepatoportal osmoreceptors and/or Na$^+$ receptors are uniquely situated for signaling Na$^+$ absorption and are likely involved in fluid and Na$^+$ homeostasis. Based on staining for c-Fos protein, it is clear that neurons located in the nucleus of the solitary tract, area postrema, and dorsal vagal complex are activated after intragastric administration of hypertonic NaCl (10). Combined, these data indicate that cells located throughout the dorsal medulla are key targets for afferent innervation from peripheral osmosensitive afferent inputs. One hypothesis is that hepatoportal osmoreceptors and/or Na$^+$ receptors play an important role in Na$^+$ homeostasis (14, 16) and may be an important factor in the development of angiotensin II-dependent hypertension. When dietary Na$^+$ is elevated, reflexes initiated from the vagal and sympathetic efferents located in the hepatoportal region act to release AVP and to inhibit RSNA. Consequently, hepatoportal afferents may evoke reflex effects that oppose angiotensin II-dependent hypertension and its centrally mediated Na$^+$ sensitivity (21).

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