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REVIEW SERIES

Negative feedforward control of body fluid homeostasis by hepatorenal reflex

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The liver, well known for its role in metabolism, clearance and storage can also be regarded as a sensory organ. The liver is an ideal place to monitor the quality and quantity of absorbed substances, because portal blood delivers substances absorbed from the intestine to the liver and these substances circulate in the hepatic vasculature before substances enter the systemic circulation. Sodium (Na^+)-sensitive mechanism exists in the liver; it is stimulated by the increase in Na^+ concentration in the portal vein, and then hepatorenal reflex is triggered. Renal sympathetic nerve activity is reflexively decreased and urinary Na^+ excretion is increased. This Na^+-sensitive hepatorenal reflex has a significant role in post-prandial natriuresis. However, the long-term role of this reflex in Na^+ homeostasis may be less important, probably because of the desensitization of Na^+-sensitive mechanisms. Na^+–K^+–$2Cl^-$ cotransporter (NKCC1) is involved in the hepatoportal Na^+-sensitive mechanism, and NKCC1 expression is reduced if the hepatoportal region is exposed to high Na^+ concentrations for a long time. This situation occurs when animals intake a high-sodium chloride diet for a long time. Liver cirrhosis also impairs the Na^+-sensitive hepatorenal reflex. Hepatoportal baroreceptor-induced renal sympathetic excitation and the impaired Na^+-sensitive hepatorenal reflex may partially explain the Na^+ retention in liver cirrhosis.
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It is well documented that the mammalian liver is not only a metabolic, clearance and storage organ but also contains many receptors, including osmoreceptors,[1,2] baroreceptors[3,4] and ionic receptors.[5–7] Given the roles that these receptors have in the systemic circulation, it is possible that they are also involved in the regulation of body fluid homeostasis. A growing body of evidence suggests that the osmoreceptors and ionic receptors in the liver and its vasculature detect a variety of physiological events and are responsible for the activation of a number of physiological responses, which may have important roles in the regulation of body fluid homeostasis. The important features of the hepatic sensor mechanism are: (1) substances consumed orally are absorbed from the intestine into the blood, circulate in the hepatic vasculature and then enter the systemic circulation; and (2) the portal venous blood flow is 20–25% of the cardiac output. Because of these features, the hepatic osmoreceptors and ionic receptors have advantages over those receptors located in the systemic circulation. First, the hepatic receptors are triggered by changes in portal venous osmolality and ionic concentration before any changes occur in the systemic blood, and then reflexively regulate renal excretion and intestinal absorption.[7–10] Second, the concentrations of the absorbed substances in the hepatoportal region and the changes in them are 4–5 times greater than those in the systemic circulation. Therefore, the hepatoportal receptors could easily detect these changes. Accordingly, the liver is the ideal place to monitor the quality and quantity of these substances and transduce them into hepatic afferent nerve activity. If the purpose of the hepatic osmo- and ionic receptors is to regulate the homeostasis of systemic body fluids, but not the portal venous osmolality or ionic concentration, they would predict the systemic blood osmolality and ionic concentration from the portal venous components. This prediction could result in errors of regulation. This error in control could be corrected by other negative feedback systems located in the systemic circulation. In this paper, we review the literature concerning the role of the liver in body fluid homeostasis.

OSMORECEPTORS OR SODIUM (NA^+) RECEPTORS IN THE LIVER

Haberich and coworkers[11,12] first suggested the existence of osmoreceptors in the hepatoportal region. Using chronically implanted conscious rats, they showed that the infusion of water into the hepatic portal vein produced a rapid increase in urine flow, whereas a similar infusion into the vena cava had less effect. Further evidence has been provided by electrophysiological studies, most of which were conducted *in situ*, with the liver perfused while the hepatic afferent nerve activity was measured.[1,2,5,13,14] Niijima[2] recorded afferent discharges from the hepatic branch of the vagal nerve of the perfused guinea pig liver, and demonstrated that increasing the perfusate osmolality with sodium chloride (NaCl) caused a dose-dependent increase in the

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discharge rate. Similar effects were produced using hypertonic Ringer solutions, prepared by the addition of mannose, glucose or sucrose. He concluded that the afferent discharge of the hepatic vagal nerve is directly related to the osmolality of the perfusate, rather than to the NaCl concentration. These results are at variance with those reported by Andrews and Orbach,[5] who suggested that only the Na^+ receptor, which is not a true osmoreceptor, is involved in the hepatic vagal afferents of the rabbit. In that study, the hepatic afferent nerve activity increased with the addition of a hypertonic solution with extra NaCl, but not with one supplemented with mannitol or sucrose.

Adachi *et al.*[1] examined 78 hepatic vagal nerve bundles in perfused rat liver and found three types of responses: the discharge rate increased in 21 bundles in response to hyperosmolality; the discharge rate increased in 14 bundles in response to hypoosmolality; and there was no response to osmotic stimulation in 35 bundles. NaCl was the most effective stimulant, although the hyperosmolality produced with urea or sucrose also activated the receptor, but the magnitude of the response was considerably less than that elicited with equiosmotic amounts of NaCl. In this context, the differences in osmolality and tonicity (effective osmolality) should be noted. Tonicity is defined as a property of a solution with reference to a particular membrane, whereas osmolality is a property of a particular solution and is independent of any membrane. However, the activity of the hepatic afferent branch of the anterior hepatic plexus increases in response to the portal venous infusion of hypertonic NaCl or sodium bicarbonate ($NaHCO_3$), but not of lithium chloride (LiCl) or mannitol (Figure 1), indicating that an Na^+-sensitive mechanism but not an tonicity-sensitive mechanism exists in the hepatoportal region.

NEUROANATOMY OF THE LIVER

The mammalian liver is innervated by both sympathetic and parasympathetic nerves, although there are many individual and species differences in their sources and distributions, and both types of nerves contain afferent and efferent fibers. These nerves enter the liver with the hepatic vasculature and bile ducts. The nerves of the liver, gall bladder and bile ducts form a plexiform structure, which is subdivided into an anterior and a posterior hepatic plexus.[15,16] The anterior plexus is located around the hepatic artery, and derives mainly from the left portion of the celiac plexus and the right abdominal branch of the left vagus, which approaches through the hepatogastric ligament. The posterior plexus is located around the portal vein and the bile duct, and derives from the right portion of the celiac plexus and the branches of the right vagus.

The vagal afferent innervation is predominantly through the left nodose ganglion and common hepatic branch, with a minor contribution through the right nodose ganglion and vagus/celiac branch. However, the major portion of the common hepatic branch does not serve the liver, portal vein or bile ducts, but innervates the duodenum, pancreas, pylorus and distal gastric antrum.[17] Spinal sensory innervation is achieved through dorsal root afferents at the thoracic spinal level of T7–T13. The question of intrahepatic afferent innervation is of central importance to the present discussion because it transmits information from the hepatic sensory receptors. However, unlike other important organs, the vagal and spinal afferent innervation of the portal and hepatic areas has not been thoroughly studied. It is generally agreed that sensory nerve fibers of either a vagal or a dorsal root/spinal origin do not directly innervate hepatocytes, but are restricted to the stroma surrounding the triads of the hepatic vasculature and the bile ducts, and to the extrahepatic portions of the portal vein and bile ducts.[18]

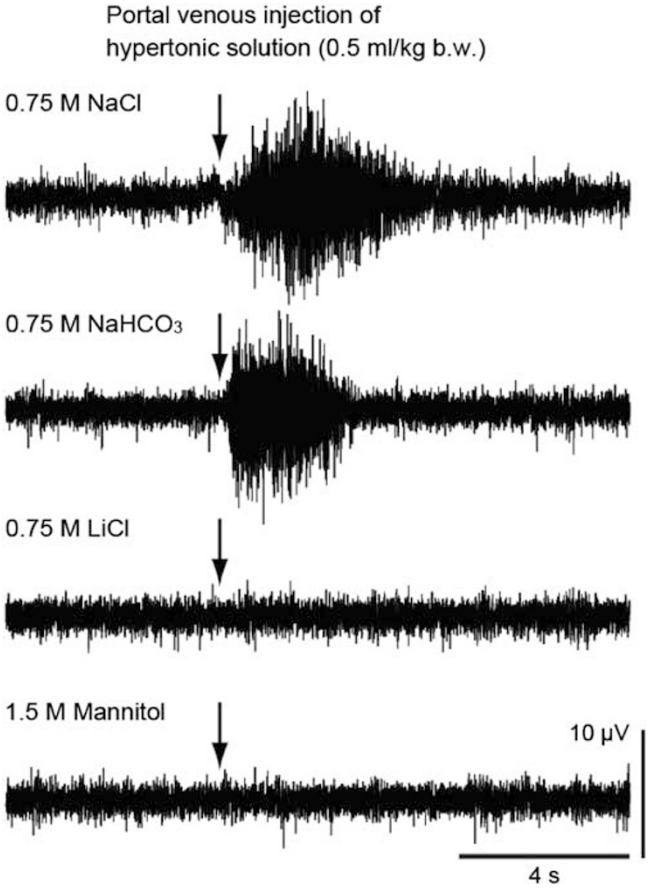

Figure 1 Original records illustrating the periarterial hepatic afferent nerve activity in response to an intraportal injection (0.5 ml kg^{-1} body weight) of hypertonic NaCl, $NaHCO_3$, LiCl or mannitol.

NA^+ RECEPTOR

The periarterial hepatic nerve responds to hypertonic NaCl, but not to hypertonic LiCl or mannitol, suggesting that it may sense the Na^+ concentration, rather than tonicity.[19] Na^+-sensitive mechanisms also exist in areas outside the hepatoportal region, that is, in the taste buds and macula densa, which sense Na^+ via the amiloride-sensitive Na^+ channel and furosemide-sensitive Na^+–K^+–$2Cl^-$ cotransporter (NKCC), respectively.[20–23] Therefore, it is possible that the hepatoportal Na^+-sensitive mechanism senses the Na^+ concentration via these Na^+ transport systems. To examine this, the responses of the periarterial hepatic afferent nerve activity to an intraportal injection of hypertonic NaCl solution were examined with or without inhibitors of the Na^+ transport systems.[6] The Na^+–H^+ exchanger and Na^+–HCO_3^- cotransporter are inhibited by amiloride and SITS (4-acetamido-4′-isothiocyanato-stilbene-2,2′-disulfonic acid), respectively, and are involved in hepatocellular pH regulation.[24,25] NKCC1 is inhibited by bumetanide, and is involved in hepatocellular volume regulation.[25,26] Bumetanide, but not amiloride or SITS, dose-dependently suppressed the hepatic afferent nerve responses to intraportal hypertonic NaCl injection, suggesting that the NKCC1 is involved in hepatoportal Na^+ sensing (Figure 2).

Although the link between the NKCC1 and the increase in hepatic afferent nerve activity is unclear, two possibilities can be considered. First, the hepatic nerve terminal might be in contact with a hepatocyte that bears NKCC1. Because NKCC1 is known to regulate hepatocellular

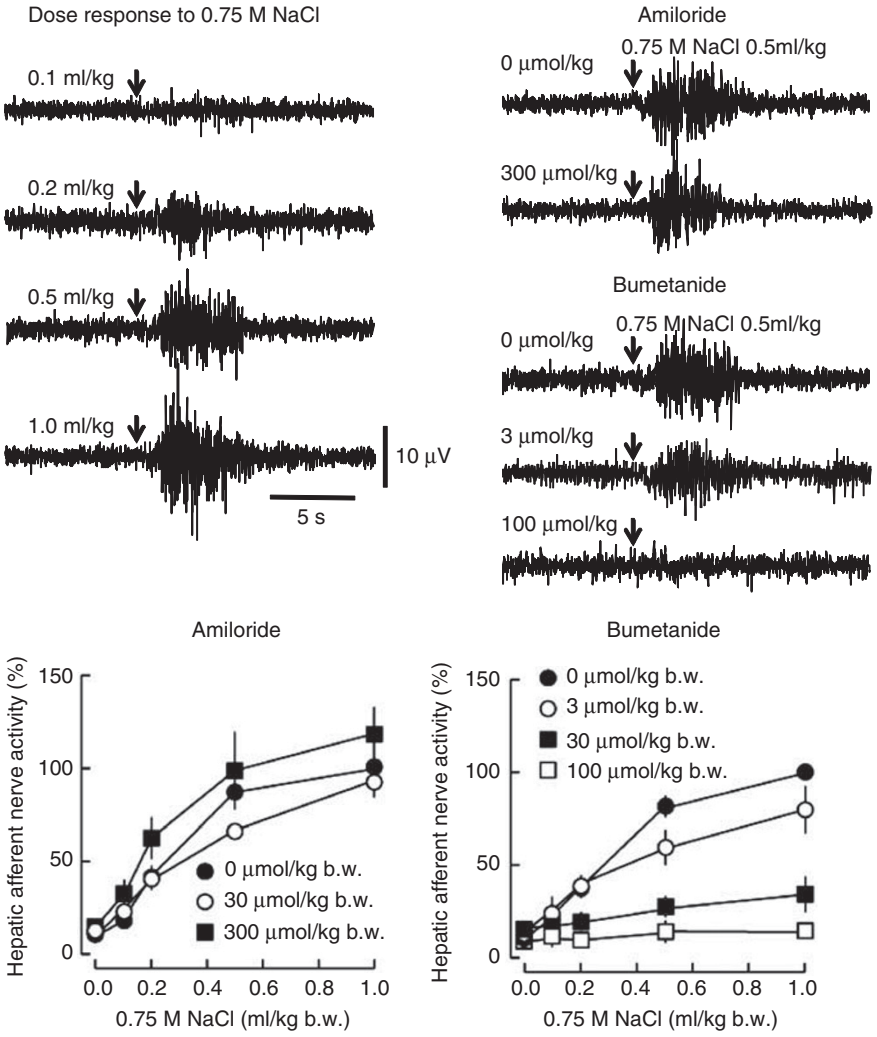

Figure 2 Upper panel: original records illustrating the hepatic afferent nerve activity in response to an intraportal bolus injection of 0.75 M NaCl (shown by the arrowheads). The left panel shows the dose-dependence of the hepatic afferent nerve activity at 0.75 M NaCl. The right panel shows the effects of amiloride (300 μmol kg^{-1} body weight into the portal vein) or bumetanide (3 and 100 μmol kg^{-1} body weight into the portal vein) pretreatment on the hepatic afferent nerve response to an intraportal injection of 0.75 M NaCl. Lower panel: summary data showing the responses of hepatic afferent nerve activity to an intraportal bolus injection of 0.75 M NaCl before and after the intraportal infusion of amiloride (left) or bumetanide (right). Modified from (Morita *et al.*[6]).

volume,[25,26] if the basolateral NaCl concentration is increased, the cellular volume will also increase, and this might stretch and stimulate the nerve terminal. Second, the nerve terminal itself might bear NKCC1, and an increase in the NaCl concentration of the portal blood might depolarize the nerve terminal. In this context, it is interesting to note that increases in the luminal NaCl concentration depolarize macula densa cells, and the alterations in the basolateral membrane potential of macula densa cells induced by changes in the luminal NaCl concentration are blocked by furosemide.[20,22,23]

CENTRAL PATHWAY

Kobashi and Adachi[27–29] extensively examined the central projection of the hepatoportal Na^+-sensitive and/or osmosensitive mechanisms. They demonstrated that certain neurons in the nucleus of the solitary tract respond to the intraportal infusion of hypertonic NaCl solution, and these units project to the caudal ventrolateral medulla, parabrachial nucleus and dorsal hypothalamus. Schmitt[30] recorded single unit activity in the hypothalamus, zona incerta (a central region that may be involved in the regulation of osmoregulatory behaviors) and ventral thalamus, and identified neurons that respond to the intraportal infusion of hypertonic NaCl solution but not to isotonic solution or a jugular infusion of hypertonic NaCl solution.

To further examine the central projection of the hepatoportal Na^+-sensitive mechanism, Fos expression was examined in response to a portal infusion of hypertonic solution.[19] In this study, the hepatoportal Na^+-sensitive mechanism was stimulated by the simultaneous infusion of 0.45-M NaCl into the portal vein and distilled water into the inferior vena cava in conscious rats, to keep the total amount of solution introduced into the systemic circulation isotonic, thus avoiding changes in the plasma osmolality and NaCl concentration. Intense Fos expression was observed in the osmoregulatory center, that is, the area postrema, nucleus of the solitary tract, paraventricular hypothalamic nucleus and supraoptic nucleus. However, few, if any Fos-positive cells were found when the rats were hepatically denervated or if they received an intraportal infusion of hypertonic LiCl or mannitol (Figure 3). Therefore, it is possible that the osmoregulatory

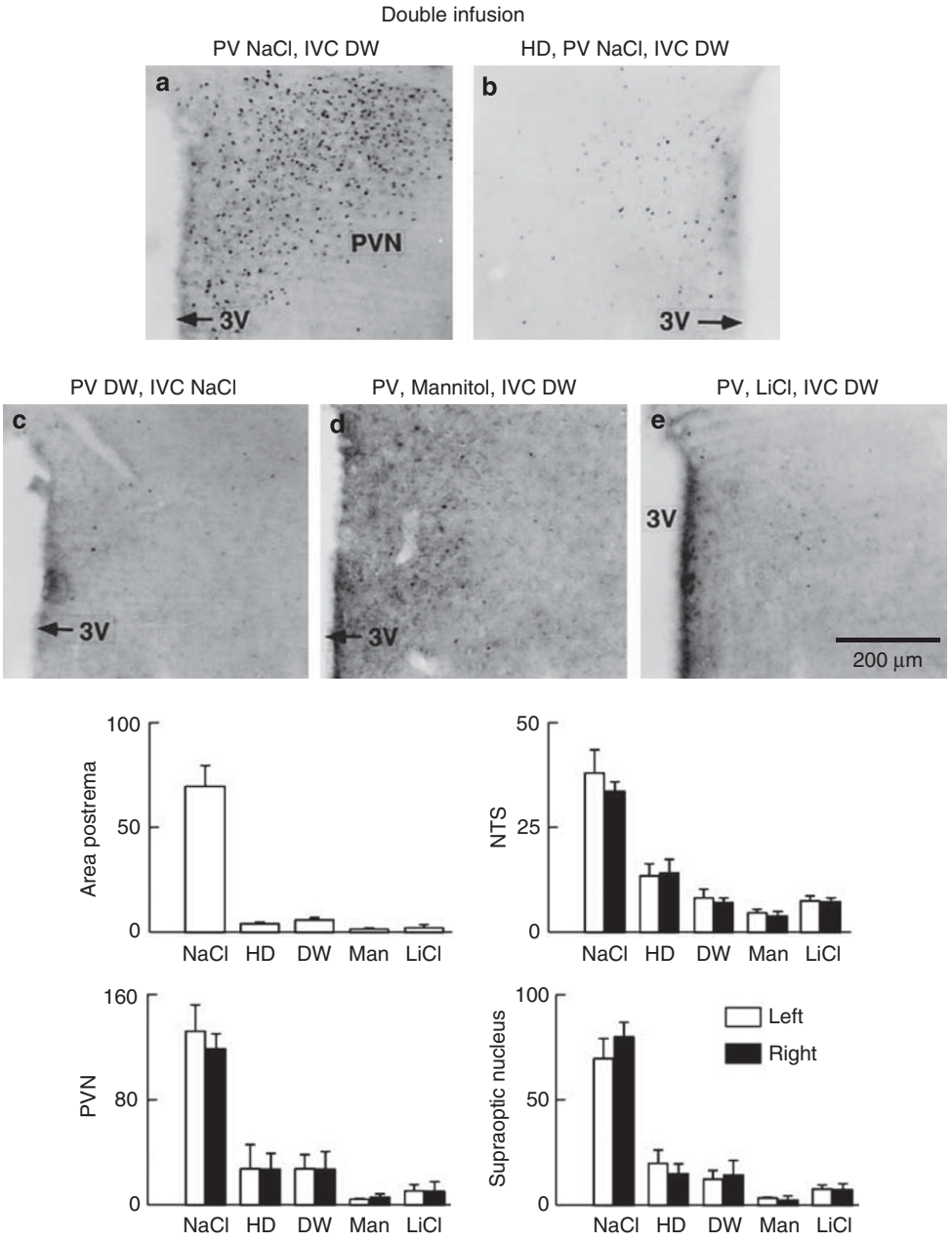

Figure 3 Upper panel: (**a**) coronal sections through the paraventricular hypothalamic nucleus of a rat simultaneously infused with hypertonic NaCl into the portal vein (PV) and distilled water (DW) into the inferior vena cava (IVC); (**b**) a hepatic-denervated rat (HD) simultaneously infused with hypertonic NaCl into the PV and DW into the IVC; (**c**) a rat simultaneously infused with DW into the PV and hypertonic NaCl into the IVC; (**d**) a rat simultaneously infused with hypertonic mannitol into the PV and DW into the IVC; and (**e**) a rat simultaneously infused with hypertonic LiCl into the PV and DW into the IVC. Lower panel: comparisons of means ± s.e.m. of Fos-positive cells from the area postrema, nucleus of the solitary tract (NTS), paraventricular hypothalamic nucleus (PVN) and supraoptic nucleus. NaCl: rats simultaneously infused with hypertonic NaCl into the PV and DW into the IVC; HD: hepatic-denervated rats simultaneously infused with hypertonic NaCl into the PV and DW into the IVC; DW: rats simultaneously infused DW into the PV and hypertonic NaCl into the IVC; Man: rats simultaneously infused with hypertonic mannitol into the PV and DW into the IVC; LiCl: rats simultaneously infused with hypertonic LiCl into the PV and DW into the IVC. Modified from (Morita *et al.*[19]).

center is activated by stimulation of the hepatoportal Na^+-sensitive mechanism, but is not activated by stimulation of the hepatoportal osmosensitive mechanism.

The intense expression of Fos in the paraventricular hypothalamic nucleus and supraoptic nucleus suggests that the stimulation of the hepatoportal Na^+-sensitive mechanism enhances vasopressin release. However, the control of vasopressin release by the hepatoportal Na^+-sensitive and/or osmosensitive mechanisms is still controversial. Intragastric hypertonic NaCl infusion, which increased portal venous osmolality but had no effect on plasma osmolality, increased vasopressin release, with significant Fos expression, in the area postrema, nucleus of the solitary tracts, supraoptic nucleus and paraventricular hypothalamic nucleus.[31] However, the vasopressin response was affected by neither subdiaphragmatic vagotomy nor splanchnic

denervation, whereas Fos expression was reduced in the nucleus of the solitary tract and area postrema by splanchnic denervation, and in the paraventricular hypothalamic nucleus and supraoptic nucleus by subdiaphragmatic vagotomy. The combined effect of vagotomy and splanchnic denervation was not examined.[32] In contrast, Choi-Kwon and Baertschi[33] reported that bilateral splanchnic denervation attenuated the vasopressin response induced by intragastric NaCl infusion by ~60%, whereas bilateral vagotomy had no effect. They concluded that the response was mediated by splanchnic afferents. Electrophysiological evidence reported by Baertschi and colleagues[34,35] supports this idea. They demonstrated that an intraportal hypertonic NaCl infusion increased the firing rates of the hypothalamoneurohypophysial tract and supraoptic nucleus endocrine neurons. Bilateral cervical vagotomy had no effect on this response, but injection of local anesthetic into the spinal cord at thoracic levels abolished the response.

HEPATORENAL REFLEX FOR NA^+ REGULATION

It is well known that the noradrenaline-containing renal sympathetic nerve terminates in the peritubular basement membrane of all renal tubular segments, as well as in the juxtaglomerular granular cells.[36] Alterations in renal sympathetic nerve activity could alter renal Na^+ excretion through changes in renal tubular transport and renin release.[37] Acute volume expansion induced with an isotonic solution reduced renal sympathetic nerve activity and then increased renal Na^+ excretion, which was attenuated by renal denervation.[38,39] The renal sympathoinhibitory response correlated well with the elevation in the left atrial pressure, and sinoaortic denervation plus vagotomy, but not sinoaortic denervation alone, completely abolished the renal sympathoinhibitory response.[38] These results indicate that isotonic volume expansion elicits renal sympathoinhibition, which is mainly mediated by the cardiopulmonary receptor with the vagal afferent. This sympathoinhibition has a significant role in augmented renal Na^+ excretion.

Intravenous hypertonic NaCl loading also induced renal sympathoinhibition and augmented renal Na^+ excretion, as did isotonic volume expansion.[9] However, the afferent pathways of the renal inhibitory responses to these two infusions (hypertonic NaCl and isotonic solutions) were different. The hypertonic NaCl-induced sympathoinhibitory response was not abolished by sinoaortic denervation plus vagotomy, but was completely abolished by the combination of sinoaortic denervation, vagotomy and hepatic denervation.[9] Therefore, the hepatic afferent nerves and the hepatorenal reflex have an important role in renal Na^+ excretion when an excess amount of NaCl is loaded.

The renal excretory response to salt ingestion is more effective than the response to an equivalent intravenous infusion of saline. This phenomenon is often referred to as 'post-prandial natriuresis'.[40,41] The renal sympathetic nerve may be involved in this natriuresis, because a portal infusion of hypertonic NaCl solution reduced the renal sympathetic nerve activity, and this reduction was abolished by hepatic denervation.[42] The role of the liver in controlling renal sympathetic nerve activity and consequently the renal excretory function was more evident in feeding experiments.[8] In chronically instrumented conscious dogs, NaCl-free food intake did not influence the plasma Na^+ concentration, renal sympathetic nerve activity or urinary Na^+ excretion, whereas high-NaCl food ($0.4\,g\,kg^{-1}$ body weight) intake increased the plasma Na^+ concentration by $3.8 \pm 0.7\,mmol\,l^{-1}$, followed by a $61 \pm 4\%$ decrease in renal sympathetic nerve activity and increased Na^+ excretion (Figure 4). In dogs with hepatic denervation, the renal sympathoinhibition seen in the intact dogs in response to high-NaCl food intake was completely abolished, and was accompanied by significantly attenuated post-prandial natriuresis. Only $9 \pm 5\%$ of the loaded Na^+ was excreted during 4 consecutive hours in the hepatic-denervated dogs, whereas $36 \pm 5\%$ of the loaded Na^+ was excreted in the intact dogs. Therefore, the hepatoportal reflex has an important role in post-prandial natriuresis.

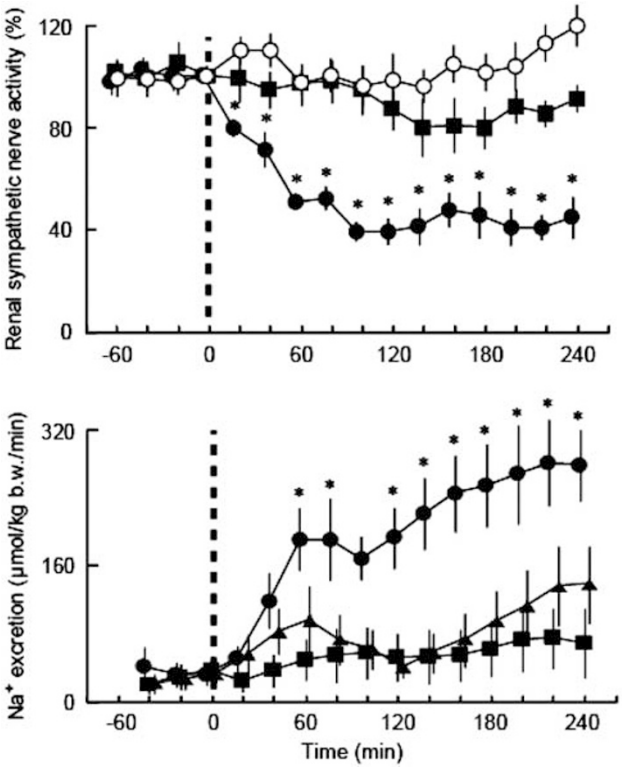

Figure 4 Upper panel: responses of renal sympathetic nerve activity in intact dogs fed a NaCl-free diet (open circles); in intact dogs fed a high-NaCl diet ($0.4\,g\,kg^{-1}$ body weight; closed circles); and in dogs with hepatic denervation fed a high-NaCl diet (closed squares). Lower panel: urinary Na^+ excretion in response to high-NaCl food intake in intact dogs (closed circles); dogs with hepatic denervation (closed squares); and dogs with renal denervation (closed triangles). Food was given at time 0. Values are means ± s.e.m. $*P<0.01$ *vs.* the pre-feeding control level. Data are modified from (Morita *et al.*[8]).

LONG-TERM ROLE FOR HEPATIC NERVES IN NA^+ HOMEOSTASIS AND ARTERIAL PRESSURE

The majority of studies that have investigated the hepatoportal Na^+-sensitive mechanism have examined the responses to transient or short-term stimulation. Although the data discussed above support the concept of a short-term role for the hepatic nerves in Na^+ regulation, few studies have examined the long-term role of the hepatic nerves. To examine this, Wistar–Kyoto rats with or without hepatic denervation were kept in metabolic cages and their Na^+ balance was measured continuously for 40 days.[43] The cumulative Na^+ balance, calculated from their Na^+ intake, urinary Na^+ excretion and fecal Na^+ excretion, stayed around 0 on a normal NaCl diet, whereas it became positive on a 3 or 8% NaCl diet (Figure 5a). Hepatic denervation had no effect on the Na^+ balance when the rats were fed a 0.45% NaCl diet. However, hepatic denervation increased the Na^+ balance to a greater extent than that observed in sham-operated rats when the rats were fed an 8% NaCl diet. At the

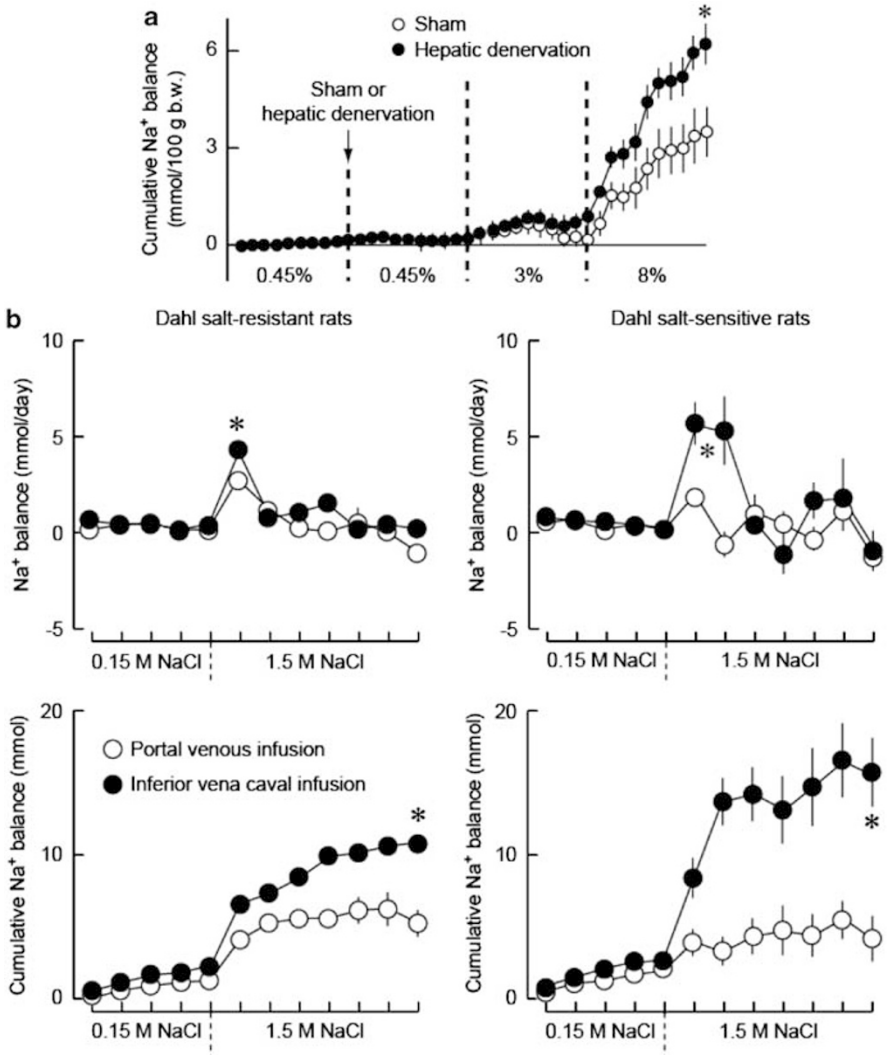

Figure 5 (**a**) Cumulative Na^+ balance before and after sham denervation or hepatic denervation in Wistar–Kyoto rats fed a 0.45, 3 or 8% NaCl diet. Each diet period was of 10 days duration. $^*P<0.05$, the response in hepatic-denervated rats is significantly different from that in sham-operated rats. Modified from (Morita *et al.*[43]). (**b**) Na^+ balance and cumulative Na^+ balance in Dahl salt-resistant (left) and Dahl salt-sensitive rats (right). Normal saline (0.15 M NaCl) was infused (0.5 ml h^{-1}) into the portal vein or inferior vena cava for 5 days and then the solution was changed to 1.5 M NaCl for 7 days. $^*P<0.05$, response after an inferior venous infusion is significantly different from that after a portal venous infusion. Modified from (Morita *et al.*[49]).

conclusion of the metabolic experiments, an arterial catheter was implanted and the arterial pressure was measured 3–5 days after implantation. The mean arterial pressure in the hepatic-denervated rats (120 ± 2 mm Hg) was slightly but significantly higher than that in the sham-operated rats (108 ± 3 mm Hg). These results suggest that hepatic denervation disrupts Na^+ homeostasis, after which exposure to a high-NaCl diet exacerbates Na^+ retention, thereby increasing the arterial pressure. However, it remains unclear whether the observed increase in arterial pressure resulted from hepatic denervation, the high-NaCl diet or both.

Carlson *et al.*[44] used telemetry measurements of arterial pressure to examine the long-term role of the hepatic nerves in controlling the arterial pressure against high-NaCl challenge. They found that hepatic denervation produced a consistent elevation of the arterial pressure in rats maintained on a normal NaCl diet (0.6%), but that hepatic denervation had little effect on the arterial pressure when Wistar–Kyoto rats were fed 8% dietary NaCl. Therefore, hepatic denervation itself causes long-term elevation of the mean arterial pressure, but does not appear to appreciably increase the arterial pressure response to a high-NaCl diet. However, it should be noted that hepatic-denervated animals lose not only the afferent nerves involved in the Na^+-sensitive mechanism, but also other afferent nerves, that is those for the baro-, glucose-, amino acid-, and metabolite-sensitive mechanisms and the efferent innervation of the liver. Therefore, hepatic denervation also influences hepatic hemodynamics through changes in the vascular tone of the hepatic artery and portal vein, in the metabolism and in biliary function[45–48]. Therefore, more-selective hepatic denervation or another experimental method that preserves the other hepatic innervation is required. To meet this requirement, 0.15-M NaCl solution was infused (0.5 ml h^{-1}) into either the portal vein or the inferior vena cave (bypassing the hepatoportal receptors) while the rats were fed low-NaCl pellets (Na^+ 0.0075 mmol g^{-1} diet), and then 1.5-M NaCl was infused for 10 days.[49] Dahl salt-sensitive rats were used in this experiment, because if they retain more Na^+ and fluid, their arterial pressure may be more highly elevated than in other rats.[50] The Na^+ retention induced by a 1.5-M NaCl infusion was more

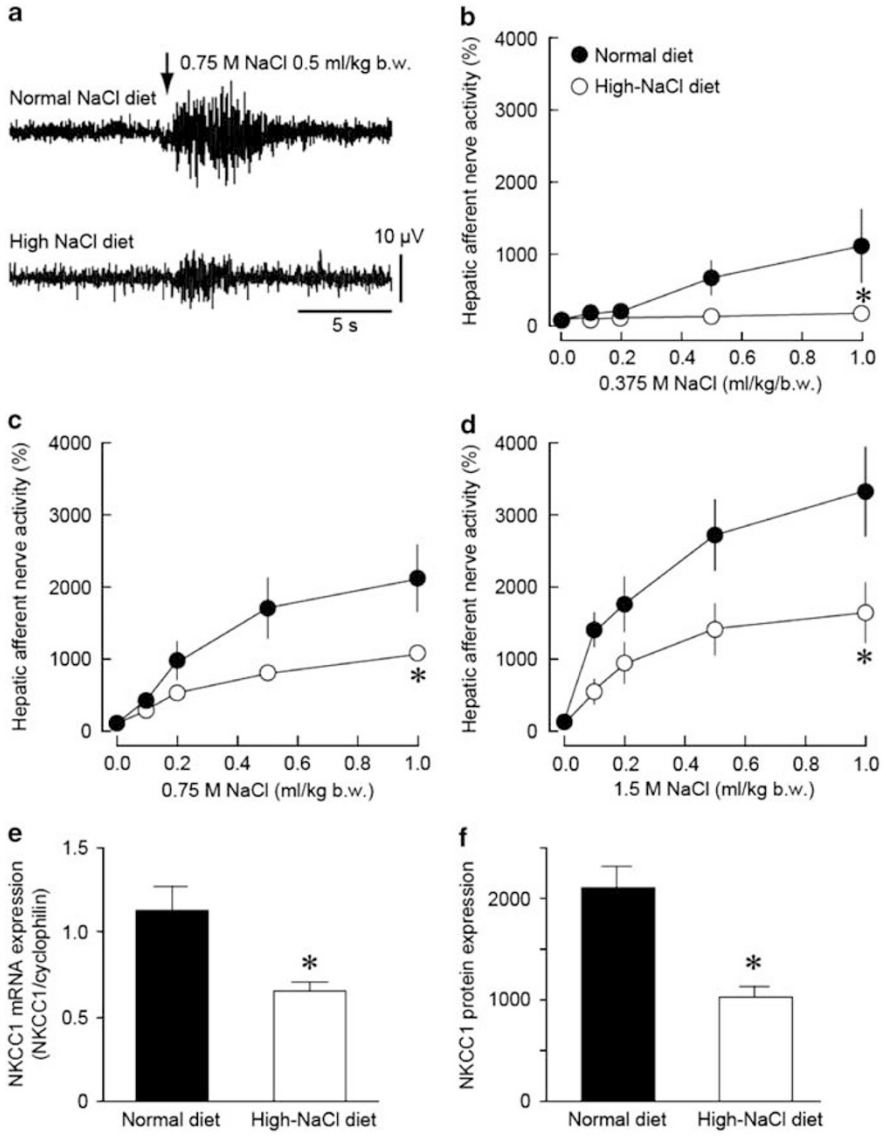

Figure 6 (**a**) Original records illustrating hepatic afferent nerve activity in response to an intraportal bolus injection of 0.75 M NaCl (shown by the arrowhead) in a rat on a normal or high-NaCl diet. (**b–d**) Summary data showing the responses of hepatic nerve activity to intraportal bolus injections of 0.375, 0.75 or 1.5 M NaCl, respectively. Values are the means ± s.e.m. for eight rats in each group. $*P<0.05$, significantly different from the normal-diet group. (**e**) Relative NKCC1/cyclophilin mRNA expression ratio in the livers of rats fed a normal or high-KCl diet. (**f**) NKCC1 protein expression (expressed in arbitrary intensity units) in the livers of rats fed a normal or high-NaCl diet. Values are the means ± SE for eight rats in each group. $*P<0.05$, significantly different from the normal-diet group. Modified from (Tsuchiya *et al.*[54]).

obvious in the inferior vena cava group than in the portal vein group, and this trend was more obvious in the Dahl salt-sensitive rats than in the Dahl salt-resistant rats (Figure 5b). This effect was only apparent for 2 days, but this positive balance was not compensated in subsequent days. Furthermore, the mean arterial pressure in the inferior vena cava group (150 ± 3 mm Hg) was significantly higher than that in the portal vein group (138 ± 1 mm Hg) in the Dahl salt-sensitive strain. However, in the Dahl salt-resistant rats, the mean arterial pressure did not differ between the inferior vena cava group (119 ± 3 mm Hg) and the portal vein group (112 ± 2 mm Hg). These results suggest that the hepatic Na^+-sensitive mechanism has a significant role in controlling Na^+ homeostasis when animals are challenged with high NaCl. Although this effect is only transient (~2 days), the resultant positive balance is not compensated thereafter.

Because a high-NaCl diet affects the expression, distribution and phosphorylation status of Na^+ transporters or channels in the kidney and intestine,[51–53] the fact that the hepatic Na^+-sensitive mechanism is only transiently significant in Na^+ homeostasis implies a desensitization or downregulation of the hepatic Na^+ receptor, NKCC1. To test this hypothesis, the expression of NKCC1 mRNA and protein and the sensitivity of the hepatic Na^+ receptor were examined after 4 weeks on a high-NaCl diet.[54] Orally ingested Na^+ is absorbed from the intestine into the blood, circulates in the hepatic vasculature and then enters the systemic circulation. Therefore, during the long-term intake of a high-NaCl diet, the hepatoportal Na^+ receptor may be continuously exposed to high concentrations of Na^+. The response of hepatic afferent nerve activity to an intraportal injection of hypertonic NaCl solution was suppressed by a high-NaCl diet (Figures 6a–d). This was

accompanied by the significantly reduced expression of NKCC1 mRNA and protein in the liver (Figures 6e and f). The high-NaCl-diet-induced reduction in the sensitivity of the hepatic Na^+ receptor is consistent with the observation that this receptor has a significant role in controlling Na^+ homeostasis only in the short-term, but not in the long-term. In other words, the reduced sensitivity of the hepatic Na^+ receptor reduces the role of the hepatic Na^+-sensitive mechanism in the long-term control of Na^+ homeostasis.

LIVER CIRRHOSIS

Renal sodium and water retention and the development of edema are the common symptoms of liver cirrhosis, and the natriuretic response to saline infusion is less pronounced in cirrhotic patients.[55] The elevated renal venous noradrenaline concentration in cirrhotic patients[56–58] suggests that augmented renal sympathetic nerve activity is a mechanism underlying the abnormal body fluid regulation in liver cirrhosis. This increase has the capacity to alter renal function by altering tubular reabsorption, renin release and renal hemodynamics, in a manner consistent with the phenomena observed in cirrhosis. In fact, a unilateral lumbar sympathetic block induces significant increases in the glomerular filtration rate, osmolal clearance, urinary Na^+ excretion, fractional excretion of filtered Na^+, and effective renal plasma flow and a reduction in plasma renin activity in patients with cirrhosis.[59] In an animal model of liver cirrhosis, more-specific renal denervation can be achieved and it has been demonstrated that bilateral renal denervation attenuates the progressive renal Na^+ retention that occurs in rats with cirrhosis induced by common bile duct ligation.[60] In that study, the cirrhotic rats retained 4.05 mmol Na^+ at the end of 1 week on a normal Na^+ diet plus 2 weeks on a low-Na^+ diet. This value was significantly greater than that recorded for sham-treated rats (1.53 mmol). In cirrhotic rats with bilateral renal denervation, Na^+ retention was significantly ameliorated (2.61 mmol). Therefore, 2.52 mmol more Na^+ was retained in cirrhotic rats than in sham-treated rats, and the augmented renal sympathetic nerve activity was responsible for approximately 57% of the Na^+ retention in the cirrhotic rats.

When studying the plasma catecholamine and central hemodynamics of cirrhotic patients, Henriksen *et al.*[61] reported that plasma noradrenaline correlated positively with the wedged hepatic vein pressure, but inversely with the plasma volume. Two possible factors were suggested as responsible for the increased renal sympathetic nerve activity in liver cirrhosis: the central blood volume and the portal pressure. Cirrhotic patients exhibit characteristic hemodynamic changes, with a hyperkinetic circulation and an abnormal distribution of the blood volume. The central blood volume decreases, despite an increase in the non-central blood volume.[62] Therefore, it is possible that the cardiopulmonary volume receptor is unloaded, and the renal sympathetic nerve is then reflexively activated.[63] Consistent with this, an increase in the central blood volume with no effect on the total blood volume, induced by head-out water immersion, which is known to reduce renal sympathetic nerve activity via the cardiopulmonary volume receptor,[64,65] significantly improves the renal excretory function.[66]

Increased hepatic portal pressure is the other factor responsible for the increased renal sympathetic nerve activity. Andrews and Palmer[67] were the first to record afferent discharges from hepatic baroreceptors. They showed that hepatic venous congestion induced by thoracic vena cava occlusion stimulated the hepatic baroreceptors and increased hepatic afferent nerve activity, whereas occlusion of the hepatic artery had no effect. When the hepatic baroreceptors were stimulated by increasing the portal pressure from 6 to 20 mm Hg, the glomerular filtration rate and renal blood flow decreased, and renin secretion increased, although the renal perfusion pressure remained constant.[68] These changes were abolished by renal denervation. Stronger evidence for the hepatorenal baroreflex was provided by Kostreva *et al.*[3] who found that increasing the intrahepatic sinusoidal pressure increased the hepatic afferent nerve activity and renal sympathetic nerve activity. Although relatively few studies have evaluated this pathway in cirrhotic patients, improved renal function and lowered noradrenaline overflow from the kidney have been observed when the intrahepatic pressure is reduced in cirrhotic patients.[69,70] These observations are consistent with the notion that the hepatoportal baroreflex contributes to increased renal sympathetic nerve activity.

In addition to the stimulation of the hepatoportal baroreflex, cirrhosis might also affect the hepatoportal Na^+-sensitive mechanisms. Lopez-Novoa and Martinez-Maldonado[71] demonstrated that the natriuretic response to the portal infusion of hypertonic NaCl solution is impaired in rats with liver cirrhosis. Stronger evidence for impaired hepatic Na^+-sensitive mechanisms was reported by Tanaka *et al.*[72] who found that the response of hepatic afferent nerve activity to an intraportal injection of hypertonic NaCl solution was suppressed in rats with carbon terrachloride (CCl_4)-induced cirrhosis (Figure 7). Metabolic experiments revealed that there was no difference in the cumulative Na^+ balance (cumulative Na^+ intake minus cumulative

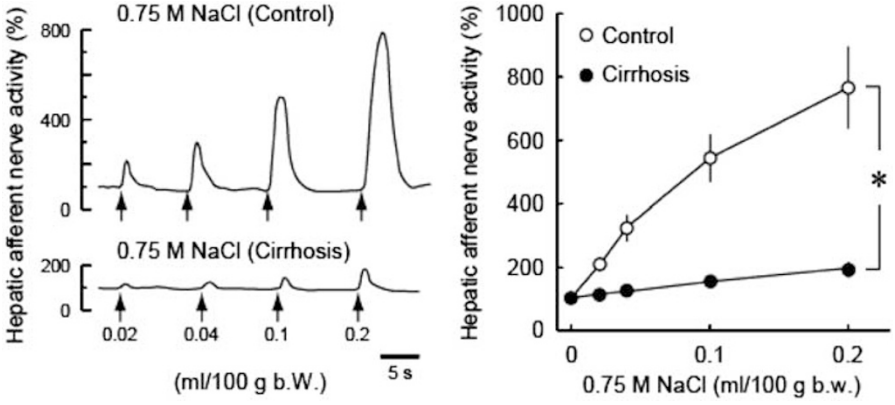

Figure 7 Left panel: typical records illustrating the response of the mean hepatic afferent nerve activity to a portal injection of 0.75 M NaCl solution. Right panel: hepatic afferent nerve activity in response to a portal injection of 0.75 M NaCl in control rats and in rats with CCl_4-induced liver cirrhosis. Values means ± s.e.m. $^*P<0.01$, significantly different from the control rats. Modified from (Tanaka *et al.*[72]).

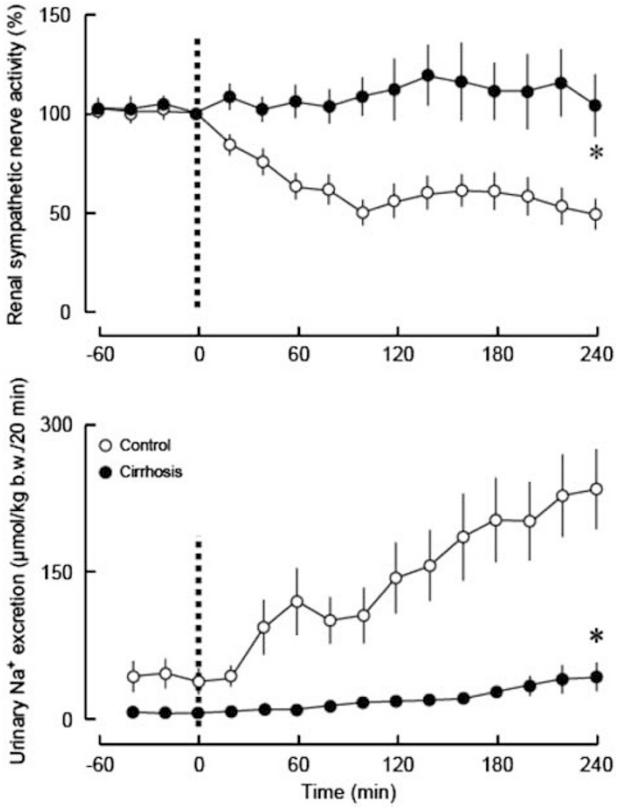

Figure 8 Responses of renal sympathetic nerve activity and urinary Na^+ excretion to high-NaCl food intake ($20\,g\,kg^{-1}$ boiled rice containing $0.4\,g\,kg^{-1}$ body weight NaCl) given at time 0. Control: sham-operated control dogs. Cirrhosis: dogs with chronic cirrhosis induced by bile-duct ligation. Values are means ± s.e.m. $^*P<0.05$, the responses in the cirrhotic dogs are significantly different from those in the control dogs. Modified from (Matsuda *et al.*[73]).

Na^+ excretion) if the cirrhotic rats were fed a normal NaCl (0.45%) diet. However, if they were fed an 8% NaCl diet, significantly more Na^+ accumulated in the cirrhotic rats.[72] Because the acute Na^+ excretory response to high-NaCl food intake is completely mediated by the hepatorenal reflex evoked by the hepatoportal Na^+-sensitive mechanism,[8] this reflex might be impaired in liver cirrhosis. This was confirmed in a feeding experiment in which conscious dogs were fed high-NaCl food ($20\,g\,kg^{-1}$ body weight boiled rice containing $0.4\,g\,kg^{-1}$ body weight NaCl) and their renal sympathetic nerve activity and urinary Na^+ excretion were measured.[73] In sham-operated control dogs, the renal sympathetic nerve activity decreased by 50% 100 min after feeding and remained at the same level until 4 h after feeding (Figure 8). Urinary Na^+ excretion increased gradually and 27% of the loaded Na^+ was excreted in 4 consecutive hours. However, the reduction in renal sympathetic nerve activity seen in the control dogs was completely abolished in dogs with cirrhosis induced by bile-duct ligation, and only 4% of the loaded Na^+ was excreted in the 4 consecutive hours after feeding. Therefore, the attenuated post-prandial natriuresis seen in the cirrhotic dogs may be attributable to the lack of the renal sympathetic nerve activity response, because post-prandial natriuresis is mainly mediated by a reduction in renal sympathetic nerve activity, as an efferent pathway.[8]

A possible explanation for the impaired hepatorenal reflex is that the function of the hepatic Na^+ receptor or intrahepatic afferent limb is impaired in cirrhosis, because cirrhosis disrupts the normal hepatic architecture, with the appearance of fibrotic bands linking portal triads and nodular regeneration. Immunohistochemical studies have shown that the nerve fibers in the liver parenchyma are reduced or nearly completely absent in cirrhotic liver disease, whereas the nerve fibers in the portal tracts and fibrous septae remain prominent.[74–76] These observations are consistent with an impaired Na^+-sensitive hepatorenal reflex, but are not consistent with hepatorenal-baroreflex-induced excitation of renal sympathetic nerve activity, because

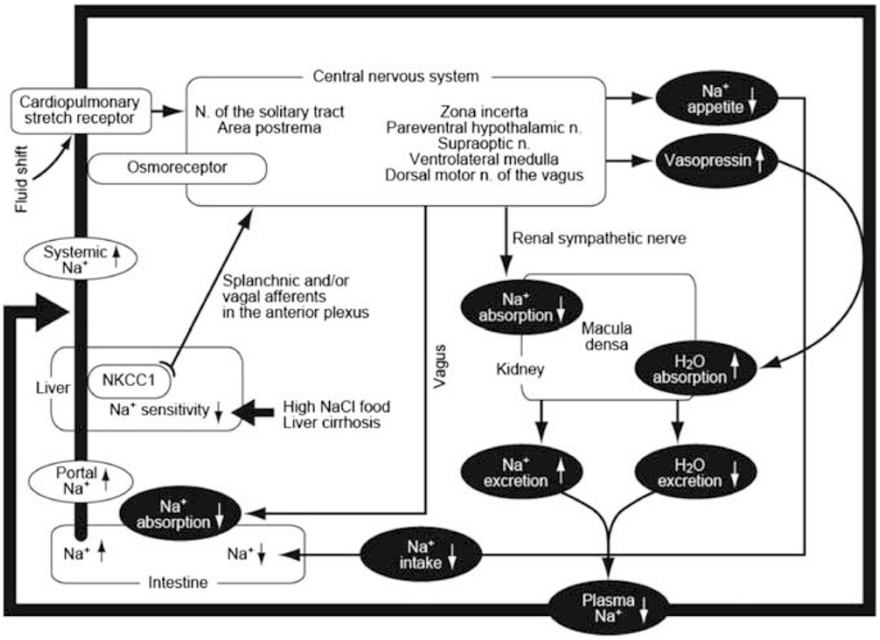

Figure 9 Schematic representation of the mechanisms involved in Na^+ homeostasis. The negative feedback systems and the hepatoportal Na^+ sensitive mechanism cooperate to regulate plasma Na^+ concentration. They may share common central and efferent pathways mediating salt appetite, intestinal absorptive function and renal excretory function. The thick line represents plasma flow from the portal vein to the systemic circulation.

reduced hepatic innervation might impair this reflex. If so, renal sympathoexcitation might not be induced. However, the increase in intrahepatic sinusoidal pressure caused by constriction of the thoracic inferior vena cava induced increases in hepatic afferent nerve activity and renal sympathetic nerve activity in both sham and cirrhotic rats. The slope gain, calculated as the percentage increase in hepatic afferent nerve activity divided by the increase in pressure, did not differ between the sham and cirrhotic rats.[77] Therefore, the hepatorenal baroreflex is even preserved well in liver cirrhosis, in which hepatic innervation is markedly impaired.

CONCLUDING REMARKS

Na^+ homeostasis is generally explained by negative feedback systems triggered by cardiopulmonary stretch receptors, Na^+ receptors in the macula densa and central osmoreceptors. Stimulation of these receptors reflexively alter salt appetite, intestinal absorptive function and renal excretory function; then changes in plasma Na^+ concentration are corrected (Figure 9). In this article, we have reviewed a second major Na^+ control system found in the hepatoportal region. Although the hepatoportal Na^+-sensitive mechanism also regulates salt appetite[49,78] and intestinal absorptive function,[10,79] this review focused on renal excretory function, that is, the hepatoportal reflex. The portal venous Na^+ concentration changes in advance of the Na^+ concentration in the systemic circulation. The hepatorenal reflex is triggered by the increase in the Na^+ concentration in the portal vein, and then controls the Na^+ concentration in the systemic blood. These observations introduce the interesting concept of negative feedforward or prospective control, that is, the Na^+ control system is activated before the composition of the systemic blood is altered.

The Na^+-sensitive hepatorenal reflex has a significant role in postprandial natriuresis. The increase in the Na^+ concentration in the portal blood is transduced into an increase in hepatic afferent nerve activity. This afferent signal is sent to the osmoregulatory center, and then renal sympathetic nerve activity is suppressed reflexively. However, the long-term role of this reflex in Na^+ homeostasis may be less important, probably because of the desensitization of Na^+-sensitive mechanisms, which occurs if the hepatoportal region is exposed to high Na^+ concentrations for a long time. NKCC1 is involved in the hepatoportal Na^+-sensitive mechanism, and NKCC1 expression is reduced by a high-NaCl diet. This observation may explain the desensitization of the Na^+-sensitive hepatorenal reflex. Liver cirrhosis impairs the Na^+-sensitive hepatorenal reflex, whereas hepatoportal baroreflex is preserved well in liver cirrhosis. Hepatoportal baroreceptor-induced renal sympathetic excitation and the impaired Na^+-sensitive hepatorenal reflex may partially explain the Na^+ retention in liver cirrhosis.

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