4.1. INTRODUCTION

Body fluid homeostasis and arterial pressure are intimately related to the point that their control share many common mechanisms. The diagram shown in Figure 4.1 illustrates an interactive network (antidehydration network) activated by the dehydration of the two major body fluid compartments, extracellular [represented by the production of angiotensin II (ANG II)] and intracellular (represented by hyperosmolarity). The operation of the network involves redundancy and reciprocity and results in effector mechanisms that counteract dehydration. Although highly simplified (many important factors, e.g., aldosterone, are omitted), the network diagram suggests complex control systems orchestrated by the brain. When deranged, the operation of such systems may lead to pathologies, for example, hypertension.

![Interactive network of signals generated by extracellular (angiotensin II) and intracellular (hyperosmolarity) dehydration and effector mechanisms (dotted boxes) that counteract dehydration (antidehydration network). Arrows only indicate the flow of information; (more...)](image)

The brain circuit that counteracts dehydration has two main entrances or input paths for sensory information arising from the periphery (blood and viscera). They are located at opposite poles of an axis of multiple connections formed between hindbrain and forebrain. The preoptic periventricular tissue surrounding the anteroventral third ventricle (AV3V) forms a key region in the forebrain pole that integrates mechanisms to control the antidehydration network. The AV3V and the lamina terminalis share the organum vasculosum (OVLT) and the ventral median preoptic nucleus (MnPO). Also belonging to the lamina terminalis is the subfornical organ (SFO). The AV3V extends from the OVLT to the periventricular preoptic tissue until the rostral limits of the anterior hypothalamic area (Figure 4.2) (Brody and Johnson 1980; Menani et al. 1988b). The OVLT, along with the SFO, functions as a primary sensory station of the forebrain that monitors humoral factors such as circulating ANG II and osmolarity (Johnson 2007; McKinley et al. 2001; Chapter 2). The other entrance to the antidehydration brain circuit is located in the hindbrain and involves primary visceral sensory inputs in the nucleus of the solitary tract (NTS) and another circumventricular organ devoid of blood–brain barrier, such as the OVLT and SFO, the area postrema (AP).
The AV3V functions as a nodal structure that integrates and redistributes signals originated in visceral sensory organs to pattern generators of neuroendocrine, autonomic and somatic effector actions against dehydration and reduction in blood volume. It has an intimate connection with the lamina terminalis and connects with many other areas in the fore and hindbrain. As suggested in Figure 4.3, signals generated in the OVLT and SFO make their way out of the lamina terminalis through projections to forebrain structures such as the paraventricular and supraoptic nuclei of the hypothalamus (PVN and SON, respectively), the lateral hypothalamus and the medial septal area (MSA) (Brody and Johnson 1980). The AV3V region also direct or indirectly connects with areas of the hindbrain that control blood pressure, including the NTS, AP and the rostral ventrolateral medulla (RVLM) (Johnson 2007; Ricardo and Koh 1978; Saper et al. 1983; Whalen et al. 1999).

The NTS and RVLM are the main areas of the medullary circuitry involved in cardiovascular control. The NTS located dorsally in the hindbrain is the site of the first synapse of baroreceptor, chemoreceptor, and cardiopulmonary receptor afferent fibers in the central nervous system, whereas the RVLM located in the ventral surface of the hindbrain is the main premotor sympathetic nuclei, projecting directly to the intermediolateral (IML) column in the spinal cord and responsible for the generation and maintenance of sympathetic vasomotor tone (Guyenet 2006). The reciprocal direct or indirect connections of the AV3V distributed along the forebrain–hindbrain axis form the neuroanatomical basis for the AV3V as an integrative region.

An important indirect connection of AV3V with hindbrain is made through the PVN, which mono- or polysynaptically connects with sympathetic neurons in IML (Westerhaus and Loewy 1999) or indirectly affects sympathetic activity through connections with the RVLM (Yang and
The role of the lamina terminalis for the sensory integration of thirst and sodium appetite has deserved a special review in a relatively recent past (Johnson 2007). In this chapter, we first briefly refresh data on the general role of AV3V on the control of body fluid homeostasis and its role for the secretion of the atrial natriuretic peptide (ANP). Then, we review more recent data emphasizing the involvement of AV3V with salivary secretion, hindbrain control of cardiovascular function, and brain plasticity, in this order. Pilocarpine, a useful cholinergic agonist for therapeutics and experimental investigation about salivation, also affects arterial pressure and fluid balance. Early evidence for a central action of pilocarpine-induced salivation derived from studies with damage to the AV3V, but now we see that the same damage also interferes with the cardiovascular effects of pilocarpine. A role for AV3V on salivation linked to thermoregulation is also discussed. Then we show how AV3V influences the control of arterial blood pressure, first by presenting its role to sustain arterial pressure taking hemorrhage as a model, and second, by discussing compelling evidence for its role in the modulation of hindbrain mechanisms involved with short-term and long-term control of arterial pressure. Finally, we recall early evidence for brain recovery from AV3V damage and its implication for brain plasticity associated with sensitization of sodium intake before leading to conclusions.

### 4.2. ELECTROLYTIC LESIONS OF AV3V: GENERAL EFFECTS ON CONTROL OF BODY FLUID HOMEOSTASIS

Damage to the AV3V produces adipsia, inhibits sodium appetite, and reduces arterial pressure and renal sodium excretion. Much of these effects may have their source in the removal of sensory and membrane protein receptors. The AV3V, especially the OVLT, but also the MnPO, is rich in receptors for ANG II. In addition, OVLT and SFO have osmoreceptors. The MnPO receives important projections from the SFO, another area rich in ANG II receptors. Several other receptors for neurotransmitters—acetylcholine, glutamate, GABA, and oxytocin—and sexual hormone receptors are located in the AV3V (Cotman and Iversen 1987; Lenkey et al. 1995; Morris et al. 1977; Simerly et al. 1990; Yamagushi and Watanabe 2005; Yamaguchi and Yamada 2008; Yoshimura et al. 1993; Chapter 2).

One of the most remarkable effects of the AV3V lesions in rats is the adipsia that occurs in the first 4 to 7 days after the AV3V lesions, without significant change in food intake (Brody and Johnson 1980; Buggy and Johnson 1977a,b, 1978; Johnson and Buggy 1978). Giving to the AV3V lesioned rats access to palatable sweet solution is an efficient method to keep the animals hydrated during the acute critical phase of adipsia. After this initial period of adipsia, rats with AV3V lesions recover most of their ad libitum daily water intake, are usually alert, move easily, and continue to ingest food and palatable solutions (Buggy and Johnson 1977a,b), thereby sustaining a regular life in the laboratory. However, although rats with AV3V lesions may also overdrink, particularly when the ratio of water to food intake is taken into account (Lind and Johnson 1983), they respond badly to challenges that affect fluid–electrolyte balance. For example, the water intake induced by different dipsogenic stimuli, such as ANG II, increased plasma osmolarity or central cholinergic stimulation is still attenuated (Buggy and Johnson 1977a,b; Menani et al. 1990). The same happens with angiotensin II–induced sodium appetite (De Luca et al. 1992).
Acute AV3V lesions also reduce the secretion of vasopressin and ANP, two hormones that mediate the control of body fluid homeostasis. They reduce vasopressin secretion and produce acute increase in urinary volume which, combined with adipsia, results in up to 25% loss in body weight, and increased plasma sodium and osmolality (Bealer et al. 1979; Brody and Johnson 1980; Buggy and Johnson 1977a). Acute AV3V lesions also reduce basal secretion of the ANP and abolish the remarkable increase in plasma ANP concentration induced by central cholinergic activation or by isotonic blood volume expansion (Antunes-Rodrigues et al. 1991, 1997; Baldissera et al. 1989). The AV3V lesion also strongly reduces ANP concentration in several forebrain areas (e.g., medial basal hypothalamus, median eminence, neurohypophysis); in the atrium, it induces a trend to decrease when acute and to increase when chronic (BaldiSSera et al. 1989). Central cholinergic-induced natriuresis strongly correlated to the increase in plasma ANP produced by the activation of central cholinergic mechanisms, and the impaired central cholinergic-induced natriuresis by AV3V lesions is correlated with the reduction of ANP in these animals. It is possible that their acute increase in plasma sodium concentration and osmolality results from combined reduction of renal sodium excretion and increased diuresis (Bealer et al. 1979; Brody and Johnson 1980; Buggy and Johnson 1977a). However, the reduced natriuresis of animals with AV3V lesions is unlikely a result of the adipsia because they still show impaired central cholinergic-induced natriuresis when pair-hydrated to sham-lesioned animals (De Luca et al. 1991).

Acute or chronic AV3V lesions block the pressor and dipsogenic responses induced by intracerebroventricular (icv) injections of ANG II and reduce or block the pressor, dipsogenic, natriuretic, and kaliuretic responses to central cholinergic activation with icv injection of the cholinergic agonist carbachol (Figure 4.4) or injection of carbachol into the SFO, MSA, ventromedial hypothalamus (VMH), and locus coeruleus (LC) (Brody and Johnson 1980; Colombari et al. 1992a,b; De Luca et al. 1991; De Luca and Menani 1996; Valladão et al. 1992). The AV3V lesions do not produce a consistent effect on the antidiuresis produced by central cholinergic activation.

**FIGURE 4.4**
(a) Increase in mean arterial pressure (MAP) and (b) water intake in sham (S) or AV3V lesioned rats (L, 2 or 12 days) treated with icv injection carbachol (7.5 nmol/1 µL) or angiotensin II (12 ng/1 1 µL). Urinary (c) sodium and (d) potassium (more...)

### 4.3. AV3V REGION: CONTROL OF SALIVARY GLAND FUNCTION AND THERMOREGULATION

Saliva spreading over the body surface when grooming is a thermoregulatory behavior of utmost importance for water balance in the rat (Ritter and Epstein 1974). Damage to AV3V reduces salivation induced by pilocarpine (Renzi et al. 1993) and heat stress (Whyte and Johnson 2002). Rats with chronic (3 weeks) AV3V lesion have higher basal core temperature and increased peritoneal temperature when ambient temperature is elevated to 37°C (Whyte and Johnson 2007). This difficulty to dissipate heat is accompanied by attenuation of cardiovascular responses—increase in arterial pressure, heart rate, and mesenteric artery resistance—to increased ambient temperature. Such impaired cardiovascular responses are not accompanied by alterations in
grooming, but by reduction in both heat-defensive behavior and salivation.

The reduced salivation to heat stress shown by animals with damage to the AV3V is likely a result of combined alterations in salivary glands and disruption of brain pathways. Acute or chronic AV3V lesions (2 to 30 days) cause atrophy of the acini, fibrosis of the connective tissue and reduced diameter of blood vessels, possibly resulting in ischemia, of the submandibular gland (Renzi et al. 1990). Those lesions also disrupt neural pathways linking all components of the lamina terminalis to hindbrain nuclei that project to the submandibular and sublingual glands (Hübschle et al. 2001). It is also possible that AV3V lesion disrupts central cholinergic pathways involved with thermoregulation (Dilsaver and Alessi 1988). Acute (first 7 days) AV3V lesions strongly impair the salivation induced by the intraperitoneal (ip) administration of pilocarpine (Renzi et al. 1993). However, in spite of the persistent morphological changes in the salivary glands, chronic AV3V lesions (15 days) produce no change in pilocarpine-induced salivation, suggesting the recruitment of alternative central pathways activated by pilocarpine to produce salivation (Renzi et al. 1993).

Pilocarpine injected systemically acts both in the brain and salivary glands to produce salivation (Takakura et al. 2003), and it is possible that damage to the AV3V alters these actions. Pilocarpine injected ip increases arterial pressure and superior mesenteric artery vascular resistance paralleled by increased blood flow and reduction in vascular resistance of the submandibular/sublingual salivary gland complex (SSG) (Takakura et al. 2005). In addition to reduced cardiovascular responses to heat (Whyte and Johnson 2007), AV3V-lesioned rats have reduced increase in arterial pressure, reduced superior mesenteric artery and hindlimb vascular resistances, and reduced SSG blood flow, in response to pilocarpine injected ip in 1 h or 2 days after the AV3V lesion (Takakura et al. 2005). The SSG vasodilation is not altered by the lesion, but it is possible that the reduced SSG blood flow contributes to the reduced salivation.

Systemic adrenoceptor antagonism and sympathetic ganglionectomy partially reduces the salivation to central pilocarpine (Cecanho et al. 1999). Therefore, disruption of sympathetic action might be a cause of the reduced pilocarpine-induced salivation in AV3V lesioned rats; however, this remains to be demonstrated.

### 4.4. IMPORTANCE OF AV3V REGION FOR RECOVERY FROM HEMORRHAGE

Intravenous infusion of hypertonic saline has been shown to successfully restore cardiovascular function in hypotensive hemorrhage (Velasco et al. 1990). The intravenous infusion of hypertonic saline rapidly shifts fluid from the intracellular compartment to the intravascular space, producing an increase in plasma volume, which seems to influence venous capacitance, improves myocardial contractility, and promotes precapillary dilation that may facilitate the recovery and survival of the animal in a hypovolemic hemorrhage. However, the increase in plasma osmolarity produced by hypertonic saline infusion may activate central mechanisms to produce vasoconstriction, which together with the peripheral mechanisms are essential for the recovery of the arterial pressure to almost normal levels.

The AV3V is involved in the central osmoregulatory control and cardiovascular responses related to ANG II, hyperosmolarity or reflex in origin (Brody and Johnson 1980; Menani et al. 1988a). It may impair the responses to central osmoreceptor activation by the hypertonic saline or the pulmonary reflexes (Lopes et al. 1981) or the central action of angiotensinergic mechanisms (Velasco et al. 1990), also suggested as being part of the mechanisms activated by hypertonic...
saline to recover the arterial pressure during a hypovolemic hemorrhage (see Chapter 8 for additional information about hypertonic saline and hemorrhage).

The AV3V lesion reduces recovery and survival to hypovolemic shock produced by hemorrhage owing to lack of ability to redistribute blood flow to essential organs (Feuerstein et al. 1984). Such susceptibility seems independent from alterations in vasopressin, renin–angiotensin, or catecholamines, but another study suggests attenuated activation of α1 adrenoceptors (Schaumloffel et al. 1990). In rats that have been bled to reach a stable arterial pressure around 60 mm Hg for at least 20 min, intravenous infusion of 7.5% NaCl (4 mL/kg of body weight) increases arterial pressure to about 100 mm Hg. As shown in Figure 4.5, the AV3V lesions (4 h to 20 days) abolish these beneficial effects of hypertonic saline on hemorrhagic shock in rats (Barbosa et al. 1990, 1992). The bleeding volume to reach the stable arterial pressure of about 60 mm Hg was similar in sham and AV3V-lesioned rats (4 h or 4 days); however, in 20-day AV3V-lesioned rats, the bleeding volume was a little smaller than that of sham rats (Barbosa et al. 1992). The reduced bleeding in 20-day AV3V-lesioned is similar to the results reported in another study in 14-day AV3V-lesioned rats (Schaumloffel et al. 1990), which suggests that differences may exist when comparing the compensatory responses during hemorrhagic shock in acute and chronic AV3V-lesioned rats.

FIGURE 4.5
Temporal evolution of mean arterial pressure (MAP) in sham- or AV3V-lesioned rats (a, 1 h; b, 4 days; c, 20 days after lesion) submitted to hemorrhagic shock by bleeding that received an intravenous infusion of isotonic (IS) or hypertonic saline (HS, (more...)

At the end of the bleeding, plasma Na⁺ concentration was reduced in sham rats, but not in AV3V-lesioned rats. The infusion of hypertonic NaCl increased plasma Na⁺ concentration in sham and AV3V-lesioned rats; however, plasma Na⁺ concentration increased more in AV3V-lesioned rats (Barbosa et al. 1992). These results suggest that AV3V lesion impairs the normal shift of fluid/solute between tissue and plasma.

4.5. IMPORTANCE OF AV3V FOR CARDIOVASCULAR RESPONSES TO ACTIVATION OF HINDBRAIN AREAS

The AV3V participates in the control of arterial pressure by affecting cardiovascular function and body fluid homeostasis as well. One of the main acute effects of the AV3V lesion is the intense tachycardia that may persist for more than 2 weeks. Most of the time, the AV3V lesions produce no significant change in the mean arterial pressure (MAP); however, a small increase in MAP may occur in some rats in the first 2 days after the lesions (Menani et al. 1988b; Vieira et al. 2004, 2006). Electrical stimulation of the AV3V produces renal and mesenteric vasoconstriction and hindquarters vasodilation associated with depressor responses and bradycardia. The vascular responses are dependent on direct sympathetic innervations and, in part, on the production of catecholamines from the adrenal gland (Fink et al. 1978; Knuepfer et al. 1984). The renal vasodilation to body fluid expansion is also modified by the AV3V lesion (see Chapter 8 for details). It is possible that these effects of AV3V lesion influence short- and long-term control of arterial pressure. Here, we focus on how AV3V influences such controls when dependent on
The pressor response produced by central angiotensinergic or cholinergic activation depends on vasopressin secretion and sympathetic activation (Hoffman et al. 1977; Imai et al. 1989), and AV3V lesions reduce vasopressin secretion and sympathetic activation produced by different stimuli (Bealer et al. 1979; Vieira et al. 2004, 2006). Moreover, cholinergic responses produced by the activation of more caudal areas such as the VMH or LC or even responses to glutamate into hindbrain areas are reduced or abolished by the AV3V lesions (De Luca et al. 1991; Valladão et al. 1992; Vieira et al. 2004, 2006). As we will show in this section, it is also possible that baseline AV3V activity releases facilitatory signals to caudal areas facilitating sympathetic activation and the pressor responses produced by the stimulation of these areas (Vieira et al. 2004, 2006).

Initial indications that the AV3V is involved with facilitation of cardiovascular reflexes integrated in the hindbrain were shown by the effect of AV3V lesions on the pressor response produced by bilateral common carotid occlusion (de Castro et al. 1993; Menani et al. 1988a). The pressor responses produced by bilateral common carotid occlusion in rats is a consequence of the deactivation of carotid baroreceptors combined with the activation of carotid and central chemoreceptors and depend on sympathetic activation and vasopressin secretion; the AV3V lesions impaired the pressor responses to common carotid occlusion by reducing sympathetic activation and vasopressin secretion activated by carotid occlusion (de Castro et al. 1993; Menani et al. 1988a).

More recently, we have shown that the AV3V also controls or modulates the effects of neurotransmission in the hindbrain with consequences to arterial pressure. The excitatory amino acid l-glutamate is one of the main neurotransmitters released by the afferent projections from peripheral baroreceptors and chemoreceptors in the NTS (Colombari et al. 1994; Haibara et al. 1995; Talman 1980). In unanesthetized rats, the injection of l-glutamate into the NTS or RVLM increases sympathetic activity and produces pressor responses (Colombari et al. 1994; Vieira et al. 2004, 2006). Acute (1 day) or chronic (15 days) AV3V lesions abolish the pressor response to l-glutamate injected into the NTS and attenuate the pressor response to l-glutamate injected into the RVLM as shown in Figure 4.6 (Vieira et al. 2004, 2006). In contrast to what they do to the more complex responses to carotid occlusion, AV3V lesions do not reduce baroreflex, chemoreflex, or vascular reactivity when evaluated separately (Bealer 1995; Vieira et al. 2004, 2006; Whalen et al. 1999). These results suggest the involvement of mechanisms dependent on the forebrain areas, particularly, the AV3V region, to facilitate the pressor responses induced by glutamatergic activation in the NTS or RVLM.

**FIGURE 4.6**

(a) Changes in mean arterial pressure (MAP) and heart rate (HR) produced by injections of l-glutamate (5 nmol/100 nL) into NTS in acute (1 day) or chronic (15 days) sham- or AV3V-lesioned rats. Changes in MAP and HR produced by injections of l-glutamate (more...)
The reduction of the pressor response to glutamate injected into the RVLM by the AV3V lesions suggests that the lesions may reduce both the glutamate-induced excitability of RVLM neurons and the resulting sympathetic activation by a yet unknown mechanism. A possible reduction in neuronal excitability of the RVLM may result from changes in basal activity or in the mechanisms activated by l-glutamate. Reduction in RVLM neuron excitability may attenuate the activation of RVLM neurons produced by l-glutamate, that is, l-glutamate does not easily activate RVLM neurons in the absence of facilitatory mechanisms dependent on the AV3V region that might increase the excitability of RVLM neurons (Vieira et al. 2006). The RVLM receives inhibitory and excitatory influences from different hindbrain and forebrain areas (Agarwal and Calaresu 1993; Dampney et al. 2003; Guyenet 2006). The AV3V lesions may produce an imbalance in those influences, by either reducing facilitatory or increasing inhibitory signals, or both, to the RVLM, thus reducing the excitability of RVLM neurons involved in sympathetic activation. In addition, besides the decrease in RVLM excitability, it is necessary to consider that AV3V lesions might also reduce the pressor responses to l-glutamate into the RVLM by directly changing the excitability of sympathetic neurons of the IML (Vieira et al. 2006). The disruption of the signals that facilitate the effects of l-glutamate into the RVLM by the AV3V lesions might be an additional mechanism that may account for the antihypertensive effects of AV3V lesions in some models of hypertension.

Anatomical connections between the NTS and the forebrain, including nuclei in the AV3V region have been described (Dampney et al. 2003; Ricardo and Koh 1978). Therefore, signals produced by l-glutamate injected into the NTS could ascend to the AV3V region, which in turn activates the sympathetic system. Similar to the effects on RVLM glutamatergic pressor responses, another possibility is that the AV3V region may send descending signals to the NTS that tonically facilitate the pressor mechanisms activated by l-glutamate into the NTS (Vieira et al. 2004). In addition to these possibilities, the reduction in the effects of l-glutamate injected into the RVLM might also be a mechanism that reduces the pressor response to l-glutamate into the NTS in AV3V lesioned rats.

Central cholinergic or angiotensinergic blockade with icv injections of the muscarinic antagonist atropine or the AT1 angiotensinergic antagonists losartan or ZD 7155 reduces the pressor response to l-glutamate injected into the RVLM similar to AV3V lesions (Vieira et al. 2007, 2010), which suggests that the effects of the AV3V lesions reducing the pressor response to l-glutamate injected into the RVLM might be a consequence of the blockade of signals produced by the baseline activation of forebrain angiotensinergic or cholinergic mechanisms.

4.5.2. Long-Term Control: Hypertension

The AV3V lesions prevents the development of experimental hypertension in different models—most of them resulting from the central action of ANG II and sympathetic activation—such as renal artery clip, aortic ligation, sinoaortic denervation, and Dahl salt-sensitive rats (Buggy et al. 1977; Goto et al. 1982; Haywood et al. 1983; Johnson 1980; Menani et al. 1988b).

The hypertension of spontaneously hypertensive rats (SHR) or the one produced by massive destruction of the NTS seems refractory to AV3V lesions (Catelli and Sved 1988; Gordon et al. 1982). Nevertheless, recent data suggest that such resistance is not absolute.

Lesions of the commissural portion of the NTS (commNTS) alone produce a transitory 7-day reduction of the arterial pressure in SHR (Moreira et al. 2009; Sato et al. 2001, 2003). Yet, as
shown in Figure 4.7, lesions of both the AV3V and commNTS produced a long-term reduction in arterial pressure that lasted until the end of the experimental period (40 days) in adult SHR (Moreira et al. 2009). This finding suggests that forebrain and brainstem mechanisms, particularly those related to AV3V region and commNTS, act together to maintain hypertension in SHR.

The treatment with intravenous AT1 receptor or ganglionic blocker produced smaller reduction in MAP in AV3V + commNTS-lesioned SHR compared to sham-lesioned SHR, which suggests that the antihypertensive effects of the combined lesions are probably related to the reduction in ANG II– and sympathetic-mediated pressor mechanisms (Moreira et al. 2009). Changes in fluid–electrolyte balance produced by the AV3V lesions or in food intake produced by commNTS lesions are not important for the antihypertensive effects of the lesions (Moreira et al. 2009). In normotensive rats, combined commNTS + AV3V lesions produced only a small and transitory reduction of MAP (less than 20 mm Hg only in the first day after lesions), which provides evidence that these lesions affect only the mechanisms activated to produce hypertension and not those that maintain normotensive levels of arterial pressure.

The AV3V lesions may affect the activity of hindbrain areas by disrupting the control the PVN exerts on sympathetic activity through direct connections with the IML or RVLM. The NTS receives important cardiovascular afferent signals and sends projections to hindbrain areas such as caudal ventrolateral medulla (CVLM), RVLM, parabrachial nucleus, and medullary regions containing catecholamine cell bodies and to forebrain areas such as specific hypothalamic nuclei (Ricardo and Koh 1978; Saper et al. 1983). Therefore, the commNTS lesion may impair important signals that control the activity of CVLM and RVLM, two main areas of the medullary circuitry involved in cardiovascular control and, in addition, also signals that might reach directly or indirectly the AV3V region. Besides the inhibitory signals that reach the RVLM through CVLM, the NTS and PVN are also important sources of excitatory inputs to RVLM and sympathetic system. Lesion of the commNTS disrupts mainly excitatory inputs from the NTS to RVLM without changing the inhibitory inputs, and AV3V lesions may impair excitatory inputs from the PVN. It seems that the blockade of both mechanisms is necessary to reduce MAP in SHR.

It seems that hypertension in SHR is strongly dependent on central complex mechanisms involving multiple central areas such as the AV3V region and the commNTS and probably different mechanisms. One mechanism may compensate for the absence of the other, which increases the probability of hypertension in these animals.

4.6. AV3V LESION: BRAIN PLASTICITY AND RESILIENCE

As already mentioned, animals with AV3V lesions are capable of recovering their daily water
intake and salivary response to pilocarpine, which is likely a result of plasticity mechanisms.

It is possible that the function to control water intake is transferred to the more lateral areas of the brain as time goes by after surgery (Gonçalves et al. 1992). Cholinergic-induced thirst by carbachol injected into medial areas such as SFO, MSA, and VMH (Colombari et al. 1992a,b; Valladão et al. 1992), but not the lateral preoptic area (LPOA), is persistently impaired by AV3V lesions. The thirst induced by carbachol injection into the LPOA is only transiently affected by AV3V lesions, suggesting that this area recovers the function to control water intake (Gonçalves et al. 1992).

It is not known what exactly is recovered through lateral areas. One possibility to check is if LPOA is linked, at least partially, to recovery of central catecholaminergic neurotransmission. Central cholinergic-induced thirst is inhibited by central injection of a beta-blocker (Saad et al. 1985), and improvement of central noradrenergic function restores water intake induced by ANG II in animals with AV3V lesions (Cunningham and Johnson 1991).

In spite of the striking impaired response to the dipsogenic and natriorexigenic effects of exogenously generated ANG II, animals with AV3V lesions still express behaviors naturally mediated by this peptide in response to water deprivation and sodium depletion (De Luca et al. 1992; Lind and Johnson 1983). Their response, however, is not as fast as that of sham-lesioned animals, and their thirst or sodium appetite is initially blunted at the beginning of sodium appetite tests. This is similar to what happens to animals with lesion of the SFO (Thunhorst et al. 1990; Weisinger et al. 1990).

The importance of AV3V and SFO is reinforced by results about cell activation, as revealed by expression of the gene c-fos. Angiotensin II and sodium depletion produces c-fos expression in all components of AV3V and SFO (Rowland et al. 1996). c-fos expression is also highly correlated with production of thirst and sodium appetite in water-deprived animals in the lamina terminalis, but particularly in the SFO of animals with hyperactive central renin–angiotensin system such as the SHR (Pereira-Derderian et al. 2010).

The importance of c-fos expression is also patent in the sensitization of sodium appetite produced by repeated episodes of sodium depletion. Angiotensin II and aldosterone are important mechanisms that subserve the sensitization of sodium appetite (Pereira et al. 2010; Sakai et al. 1987), and enhanced c-fos expression in the SFO is correlated with the enhanced sodium appetite of animals with history of sodium depletion (Na et al. 2007). Enhanced activity in an important area to control sodium intake and sensitive to ANG II, such as the SFO, plus morphological alterations in spiny neurons in the nucleus accumbens (Na et al. 2007; Roitman et al. 2002) suggest a neural basis to the enhanced sodium appetite. However, AV3V lesioned animals submitted to multisodium depletions are capable of enhancing both their sodium appetite to restore sodium deficit acutely as well as their need-free daily hypertonic sodium intake, as sham-lesioned animals do (De Luca et al. 1992).

It is also possible that in spite of the strong link between the effects of ANG II and the AV3V, redundant mechanisms may take hold to control water and sodium intake when this region is damaged. For example, in addition to the LPOA mechanism (Gonçalves et al. 1992), the AV3V lesioned animals remain responsive to the natriorexigenic effect of deoxycorticosterone, which mimics the effect of aldosterone (De Luca et al. 1992; Fitts et al. 1990). Moreover, similar to what happens when combined lesions of AV3V and commissural NTS reduce the arterial
pressure of SHR (Moreira et al. 2009), combined lesions of the OVLT and SFO are more effective than single lesions to reduce sodium appetite (Fitts et al. 2004). This suggests neural redundancy outside and within the lamina terminalis itself. Finally, ANG II belonging to renin–angiotensin systems localized in other parts of the brain (Wright et al. 2008) might also contribute to redundancy, particularly to long-term mechanisms such as those related to behavioral sensitization; however, remains to be checked.

4.7. CONCLUSIONS

The AV3V broadly participates in the control of behavioral and physiological responses related to fluid–electrolyte balance, thermoregulation, and cardiovascular function. Several of such responses depend on sensory information that enters the brain through the lamina terminalis. Several others result from the activation of different forebrain areas. More specifically, in the forebrain, the AV3V region processes sensory information that arises from circulating humoral factors, and its damage makes animals insensitive to the effects of ANG II and increased osmolarity. The AV3V is also necessary for responses to forebrain cholinergic activation such as thirst, natriuresis, ANP release, and increase in arterial pressure and salivation.

In addition to its importance as an integrative area for forebrain mechanisms, it is interesting to note the strong connections between the AV3V and the hindbrain circuitry involved with the control of sympathetic activity. Although baseline sympathetic activity and arterial pressure in normotensive rats do not seem to depend on AV3V signals, sympathetic activation produced by different stimuli acting at different levels of the central nervous system are strongly dependent on the AV3V, including the sympathetic activation produced by the glutamatergic stimulation of the NTS–RVLM circuitry that directly activates the sympathetic neurons. Another good evidence of the connections between the AV3V and the hindbrain pressor mechanisms is the chronically persistent reduction of the hypertension in SHR by the combined AV3V and commNTS lesions, an effect not produced by the lesion of each area alone. In addition, the AV3V is also essential for the activation of hypertensive mechanisms in many models of experimental hypertension and is part of the central circuitry that sustains arterial pressure in response to body fluid challenges such as hemorrhage, all indications of the importance of the AV3V for the activation of pressor mechanisms.

The importance of the AV3V for signals originating at different poles of the brain suggests it works as an integrator of autonomic mechanisms by processing information along an axis between the forebrain and the hindbrain. The impact of AV3V lesions on several aspects of body fluid balance and cardiovascular function are summarized in Table 4.1. The recovery and resilience of some of those aspects suggest plastic and redundant phenomena waiting for further experimental scrutiny.

### TABLE 4.1

Effects of Acute and Chronic AV3V Lesions in Cardiovascular System and Fluid–Electrolyte Balance

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