Differential effects of dorsomedial medulla lesion size on ingestive behavior in rats

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Wang, Tianlun, and Gaylen L. Edwards. Differential effects of dorsomedial medulla lesion size on ingestive behavior in rats. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1299–R1308, 1997.—Previous studies indicate that rats with lesions centered on the area postrema (AP) drink more saline and consume abnormally large amounts of water after treatment with subcutaneous isoproterenol (Iso) or angiotensin II. In addition, lesioned rats lose a significant amount of body weight immediately after surgery. Nonetheless, there are disparate reports on the effects of lesions of the AP on fluid intake and body weight. These reports suggest that the adjacent nucleus of the solitary tract (NTS) may play a role in the effects observed subsequent to the lesion. In this study we evaluated the effects of varying lesion size on body weight, fluid intake, and the baroreflex. As the lesion included more of the NTS, the effect on body weight was reduced. Moreover, water intake induced by Iso increased as more NTS was involved in the lesion. Conversely, 3-h ad libitum saline intake and saline intake after sodium depletion decreased with more involvement of the NTS in the lesion. These data suggest that the neural population in the NTS bordering the AP may play a critical role in the control of water and saline intake as well as the regulation of body weight.

METHODS

Animals and Housing

Adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) initially weighing ~250 g were the subjects of all experiments. Animals were housed in suspended stainless steel cages in a temperature-controlled room on a 12:12-h light-dark cycle, with lights on at 0700. The rats consumed pelleted food (Purina Mills, St. Louis, MO) and tap water ad libitum except during drinking tests, when food and water bottles were removed and calibrated drinking tubes with metal sipper spouts were placed on the cage.

Surgical Procedures

Forty-two animals were divided into three groups: 1) rats with lesions of the AP and minimal involvement of the adjacent NTS [small lesion group (Sx), n = 14], 2) rats with lesions of the AP involving a significant amount of the adjacent NTS [large lesion group (Lx), n = 12], and 3) sham-operated rats (CT, n = 16). Behavioral testing data from all animals were included in the statistical analysis. Surgery was accomplished by initial anesthetization of each rat with methoxyflurane (Metofane, Pittman-Moore). The dorsum of the head and neck was shaved and vacuumed. The surgery was accomplished by initial anesthetization of each rat with methoxyflurane (Metofane, Pittman-Moore). The dorsum of the head and neck was shaved and vacuumed. The rat was placed in a stereotaxic instrument, and the skin was disinfected with chlorhexidine (Nolvasan, Fort Dodge, IA). The skin was incised from a point just rostral to the occipital crest to the midcervical region, and the muscles were dissected to expose the atlantooccipital ligament. This ligament and the underlying dura mater and arachnoid membrane...
were incised to expose the dorsal surface of the medulla. The AP was visualized through a dissecting microscope. The small lesions were produced by aspiration of the AP with a 30-gauge blunt stainless steel tube connected to a vacuum line. The larger lesions, involving a significant amount of the adjacent NTS, were prepared by aspiration of the AP and part of the adjacent NTS with a 23-gauge blunt stainless steel tube. Sham lesions were produced by exposing the AP and gently touching the surface of the brain with a cotton swab. The musculature and the skin of the surgical wound were closed with absorbable and nonabsorbable suture, respectively. After surgery, body weights were monitored daily for the first 15 days and at least three times weekly thereafter. Behavioral studies were not started until at least 20 days after surgery. The sequence of behavioral tests is in the order presented in the following text. Animals were tested no more than three times a week, with at least 1 day between each of the tests.

Behavioral Testing

Water intake. Twenty-four-hour tap water intake, with pelleted food present, was measured for 2 days. In addition, all groups were tested for 3-h distilled water intake after dipsogenic challenges. The challenges included subcutaneous administration of 25 µg/kg ISO to mimic depletion of the extracellular fluid space (26) and 1 mL/100 g body wt 6% hypertonic saline to produce cell dehydration. All testing was performed at approximately midlight phase of the light-dark cycle, in the absence of food, and calibrated drinking tubes were presented on the cages in the place of water bottles. The animals were given a 30-min acclimation period before each challenge. Intakes after injection of ISO or hypertonic saline were compared with intakes after treatment with an equivalent volume of physiological sterile saline (PSS), i.e., 1 mL/kg and 1 mL/100 g body wt, respectively. Three-hour distilled water intake was also evaluated with no treatment and after 24-h water deprivation with food present.

Saline intake. Ad libitum intake of 1, 2, and 3% saline was measured for 3 h during the light phase of the light-dark cycle. Three-hour 3% saline intake after sodium depletion was also measured. Sodium depletion was accomplished by subcutaneous injection of 10 mg/kg of furosemide (2 times, 2 h apart) accompanied by food replacement with a low-sodium diet (0.3%) for 24 h before testing.

Feeding behavior. The feeding studies examined conditioned taste aversion (CTA) learning and also served as an antemortem analysis of the AP lesion. We tested animals for development of CTA to a novel food using paraquat as the unconditioned stimulus (UCS). An earlier report indicated that an intact AP is required to produce CTA when paraquat is used as the UCS (6). This behavioral test has been previously used to evaluate the completeness of AP and immediately adjacent NTS lesions (11). Animals were first trained to drink sweetened condensed milk during 30-min test periods for 2 days. On CTA test day 1, all the rats were presented with a novel flavored diet, almond-flavored sweetened condensed milk, for 30 min, and their intake was recorded (conditioning trial). Immediately after the 30-min trial period, the animals were subcutaneously injected with 15 µmol/kg paraquat. Seventy-two hours later, rats were presented with almond-flavored sweetened condensed milk, and their intake was measured for 30 min (retention trial). Animals that had developed a CTA consumed little or no milk, whereas animals that had not developed an aversion consumed as much or more milk than they consumed on CTA test day 1.

Baroreflex Testing

Once CTA testing was complete, the baroreflex was examined in 30 conscious rats. The baroreflex was not measured on the remaining 12 rats because of the failure of catheters. Baroreflex testing provided a functional measure of damage to the more lateral portions of the caudal NTS, where most high-pressure baroreceptor afferents synapse (13). Femoral arterial and venous catheters were placed while the animals were under Metofane anesthesia. The femoral arterial catheter was prepared from polyethylene tubing (PE-50). The femoral venous catheter was made from Silastic tubing (0.02 in. ID, 0.037 in. OD). Both catheters were tunneled subcutaneously to exit at the base of the neck. The rats were allowed to recover from surgery for ~3 h before baroreflex testing began at 1800–2000. The arterial and venous catheters were connected by lengths of cuffed PE-50 to a blood pressure transducer and a 5-ml syringe on an infusion pump (model A-99, Razel Scientific Instruments, Stamford, CT), respectively. The blood pressure and heart rate (HR) were recorded by a Digi-Med blood pressure analyzer (Micro-Med, Louisville, KY). The digital data were transmitted from the analyzer to a computer. Arterial baroreflex inhibition of HR was produced by using stepwise increasing infusions of phenylephrine (i.e., phenylephrine hydrochloride, 0, 2, 4, 6, 8, 10, and 12 µg/kg body wt/min, 2 min each; Sigma, St. Louis, MO). Baroreflex function was analyzed by plotting the change in HR vs. the change in blood pressure and determining the slope of the regression line.

Histology

Once baroreflex testing was complete, each rat was transcardially perfused with phosphate-buffered saline followed by buffered 4% paraformaldehyde. The brain was removed and postfixed for 2–3 h in buffered 4% paraformaldehyde with 10% sucrose. The brain was then cryoprotected by immersion in 30% sucrose for ~48 h. The brains were frozen, and 30-µm coronal sections were prepared on a cryostat. The sections were mounted continuously in order on gelatin-coated slides and were stained with cresyl violet.

Image Analysis to Determine Lesion Volume

The slides were viewed on a Nikon microscope connected to a computer with image-analysis software (Image-Pro Plus). A digitized image was acquired from the microscope, and the area of the AP and the intermediate and subpostremal NTS between the two solitary tracts was measured. The range of the intermediate and subpostremal NTS included in the analysis extended ~0.80 mm rostral and 0.85 mm caudal to obex (Fig. 1). The total volume of the AP and the NTS was calculated by summation of the area of each section multiplied by 30 µm (section thickness). The percentage of the AP and NTS remaining in lesioned animals was obtained by dividing the volume of the remaining AP and NTS of each lesioned rat by that of a representative sham-lesioned intact rat.

Statistical Analysis

All the intake data were expressed and analyzed as the intake per metabolic body size (MBS), that is, body weight in 100 grams raised to the power of 0.75. Linear regression and correlation were performed, with percentage of remaining NTS volume as the x variable and behavioral data as the y variable. Statistical analysis of behavioral data was performed with the use of repeated measures analysis of variance (ANOVA).
groups of lesioned rats were significantly less than the Bx animals (\( P < 0.001 \)). Body weights of the Sx rats were significantly less than those of CT animals at this time (\( P < 0.001 \)). This pattern persisted throughout the study period (\( P < 0.001 \)). Linear regression and correlation analysis indicated that body weights of lesioned rats had a significant negative correlation with the amount of remaining NTS (Table 1; \( P < 0.001 \)). In other words, as the lesion size increased, the magnitude of the body weight loss decreased.

Behavioral Testing

Water intake. Water intake by Sx and Bx rats was significantly more than that of CT rats on a 24-h basis when expressed relative to body size [(in ml/MBS) Sx, 19.6 \pm 2.1; Bx, 19.8 \pm 1.6; CT, 12.0 \pm 0.6; \( P < 0.02 \)]. On the other hand, absolute 24-h water intake was not significantly different [(in ml) Sx, 26.1 \pm 3.2; Bx, 32.6 \pm 2.7; CT, 28.4 \pm 2.9; \( P > 0.30 \)]. No statistically significant difference in 3-h water intake was noted between groups after 24-h water deprivation when expressed relative to body size [(in ml/MBS) Sx, 6.0 \pm 0.8; Bx, 5.1 \pm 0.6; CT, 4.7 \pm 0.2; \( P > 0.40 \)]. Likewise, absolute 3-h water intake after 24-h water deprivation was not different (\( P > 0.07 \)).

After subcutaneous injection of 1 ml/kg PSS, both lesioned groups drank more than the CT group over the entire 3-h test period; however, Sx rats drank significantly more water than Bx rats during the first 30-min and 60-min periods (Fig. 5A; \( P < 0.05 \)). After Iso treatment to activate the renin-angiotensin system, water intake was increased over water consumption during the baseline test when 1 ml/kg PSS was injected in all groups (\( P < 0.007 \)). Starting at 30 min and persisting across the entire 3-h time course, the increase in water intake by Bx rats was significantly greater than that of Sx rats and CT rats, whether expressed relative to body size (Fig. 5B; \( P < 0.001 \)) or in absolute terms (\( P < 0.001 \)). It is also important to note that the amount of Iso-stimulated water consumption was negatively and significantly correlated with the amount of intact NTS of lesioned animals (Table 1; \( P < 0.015 \)).

After the rats were challenged with subcutaneous 1 ml/100 g body wt 6% hypertonic saline to produce intracellular dehydration, water intake was enhanced significantly over water consumption during the baseline test when the rats were treated with 1 ml/100 g body wt PSS (\( P < 0.005 \)). The amount of increased intake by lesioned groups was significantly greater than that of the CT group when expressed relative to body size (Fig. 6; \( P = 0.007 \)). The absolute amount of increased water intake produced by hypertonic saline was not significantly different between the groups (\( P > 0.09 \)). Linear regression and correlation analysis indicated the existence of negative correlation between the amount of increased intake and the volume of the intact NTS for both means of expressing water intake (Table 1; \( P < 0.05 \)).

Saline intake. Three-hour ad libitum 1, 2, and 3% saline intake in Sx rats was significantly greater than that in Bx rats. Both groups consumed significantly more saline than the CT group (Fig. 7; \( P < 0.001 \)).
Significant differences were evident at 30, 60, 120, and 180 min (P < 0.05). Additionally, there was a positive correlation between ad libitum saline intake and the amount of intact NTS (Table 1; P < 0.05).

Twenty-four hours after furosemide injection and administration of low-sodium diet to produce sodium depletion, saline intake by Sx rats remained elevated over Bx rats. Furthermore, 3% saline intake during
this test was positively correlated with the volume of intact NTS (Table 1; P < 0.05). Although intake by only the Sx group was significantly greater than the CT group after depletion (Fig. 8; P < 0.02), sodium depletion increased saline intake over the baseline intake only in the CT group (P > 0.05). This is not in agreement with observations from earlier studies in which the increase in saline intake produced by sodium depletion was comparable between rats with lesions of the AP and control rats (7).

Feeding behavior. Before paraquat injection, the consumption of almond-flavored sweetened milk by rats with both Sx and Bx lesions was significantly greater than the intake of CT rats (Fig. 9, P < 0.001). Seventy-two hours after paraquat treatment, consumption of the almond-flavored milk, the conditioned stimulus, was reduced in CT rats, indicating a CTA to almond-flavored sweetened condensed milk (Fig. 10). However, which the increase in saline intake produced by sodium depletion was comparable between rats with lesions of the AP and control rats (7).

Table 1. Linear regression and correlation between behavior and percentage of remaining NTS

<table>
<thead>
<tr>
<th>BW, body wt 21 days after surgery. Iso, increased 3-h water intake over baseline intake after isoproterenol treatment; HS, increased 3-h water intake over baseline intake after 6% hypertonic saline treatment; WD, 3-h water intake over baseline intake after 24-h water deprivation; NTS, nucleus of the solitary tract.</th>
<th>Water Intake</th>
<th>Ad Libitum Saline Intake</th>
<th>3% Saline Intake After Depletion</th>
<th>Milk Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BW</td>
<td>Iso</td>
<td>HS</td>
<td>WD</td>
</tr>
<tr>
<td>r²</td>
<td>0.44</td>
<td>0.22</td>
<td>0.37</td>
<td>0</td>
</tr>
<tr>
<td>Slope</td>
<td>-131.51</td>
<td>-1.54</td>
<td>-7.40</td>
<td>0.26</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.02</td>
<td>0.02</td>
<td>0.87</td>
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</table>

Fig. 3. Percentage of remaining intermediate and subpostremal NTS between 2 ts. aSignificantly different from sham lesions (CT, n = 16, P < 0.001). bSignificantly different from small lesions (Sx, n = 14, P < 0.001). Bx, large lesions (n = 12). Data are expressed as mean percentage of NTS remaining ± SE.

Fig. 4. Body weights of Sx (n = 14), Bx (n = 12), and CT (n = 16) rats over 60-day period after surgery. Note significant body weight loss by both lesioned groups. However, Sx rats lost significantly more body weight than Bx rats. a, Significantly different from CT (P < 0.001). b, Significantly different from Bx (P < 0.001).

Fig. 5. A: water intake after sc injection of 1 ml/kg physiological sterile saline. a, Significantly different from CT (P < 0.001). b, Significantly different from Sx (P < 0.001). B: increase in 3-h water intake over baseline intake after sc isoproterenol injection. Data are mean increased water intakes [ml/metabolic body size (MBS)] ± SE.
Sx rats as well as Bx rats drank as much or more milk during the retention trial, indicating that they failed to develop a CTA. These results support the histological evaluation of the lesion in that they provide functional evidence of the completeness of the AP lesions.

Table 2 summarizes the data from analysis of mean arterial blood pressure (MAP) and HR collected at 10-s intervals. No significant difference in baseline MAP and HR was observed between groups. When 12 µg·kg⁻¹·min⁻¹ phenylephrine was infused intravenously to increase blood pressure, and increased blood pressure reflexively decreased HR, there was a significant increase in MAP in all groups ($P < 0.001$), although Bx rats tended to have a smaller elevation in MAP. HR was significantly reduced in all groups ($P < 0.02$). There was a tendency for a greater reduction in the CT group, but this was not statistically significant. Linear regression analysis of baroreflex indicated that the slope tended to be smaller in lesioned rats than in CT rats and that the Bx rats had the smallest slope, although these differences were not statistically significant. The above observation suggests the possibility that the lesion may have impinged on the tissue surrounding the AP that receives baroreceptor afferent input. Importantly, we noted that during baroreflex recording, HR occasionally increased in the lesioned animals when the blood pressure was enhanced by phenylephrine infusion. In the linear regression and correlation analysis, $r^2$ represents the proportion of the total variability of the $y$ values that is accounted for by the independent variable $x$. The instability of baroreflex, as reflected by the smaller $r^2$ value of the linear regression analysis of baroreflex, further suggests that the lesions may have impaired the reflex.

**DISCUSSION**

Previous studies that used thermal lesions centered on the AP reported a greatly enhanced water intake in response to Iso treatment (10). However, in a recent study (33) this enhanced drinking was not observed in...
rats with aspiration lesions of the AP. Comparison of the histology of lesions from the more recent studies with previous lesions indicated that the earlier lesions included more of the NTS than recent lesions. The present study quantitated lesion size, and the results indicate that rats with lesions of the AP, as well as in a significant amount of the adjacent intermediate and subpostrema NTS, exhibit increased drinking behavior after subcutaneous Iso. Thus damaging a significant amount of NTS adjacent to the AP is necessary for expression of overdrinking behavior to Iso. This observation is interesting with regard to the anatomic observation that glossopharyngeal and vagal nerve fibers terminate heavily in the caudal NTS, whereas only vagal fibers enter the AP (2). It is possible that rats with lesions of the AP and a significant amount of the adjacent NTS lost secondary afferent neurons for low-pressure cardiopulmonary baroreceptors in the NTS. Thus transmission to higher brain structures from these receptors could possibly be interrupted. This may result in the lesioned rats having exaggerated drinking responses. This speculation is supported by previous behavioral data. It has been shown that expansion of the wall of right atrium where low-pressure cardiopulmonary receptors are located inhibits water intake (16). Moreover, it is reported that bilateral lateral parabrachial nucleus (LPBN) lesions attenuate the inhibitory effect of right atrial expansion on drinking after Iso administration (24). Bilateral LPBN lesions produce an enhancement in drinking behavior similar to lesions of the AP with significant damage to the NTS in rats (8, 10, 23). Because LPBN lesions attenuate inhibition of drinking by activation of cardiopulmonary receptors, it is plausible that lesions of the AP with significant NTS damage would also attenuate the inhibitory effect of right atrial expansion.

On the other hand, it is possible that large lesions encroach more laterally into the caudal NTS such that more of the secondary high-pressure baroreceptor neurons are destroyed, resulting in impairment of the baroreflex. Iso is a β-adrenergic agonist; thus it activates the renin-angiotensin system by directly stimulating juxtaglomerular cells in the kidney and by decreasing blood pressure. It is hypothesized that peripherally synthesized ANG II acts on the brain at the subfornical organ to generate thirst after Iso treatment (12). Because Iso also results in hypotension by vasodilation, the drop in blood pressure in Bx rats may not be corrected by increases in HR as in intact rats because of an impaired baroreflex. This latter possibility seems unlikely because the baroreflex appeared functional in this study.

We did observe an enhanced intake of water after hypertonic saline challenges in rats with lesions of the AP. However, this enhancement is only apparent if the water intake is expressed relative to body weight. If water intake is expressed as absolute water intake, there is no difference between groups. Thus our observations are similar to previous studies that reported absolute water intake and found no difference in water intake after hypertonic challenges (10). In the case of Iso-induced drinking, there is an increase in absolute water intake in rats with lesions of the AP. Thus lesions of the AP do appear to influence water intake induced by mechanisms related to extracellular dehydration to a greater extent than by mechanisms related to intracellular dehydration.

Similar to the observation of Contreras and Stetson (4) in 1981, we found that 3-h ad libitum saline intake in rats with lesions of the AP and a small amount of the adjacent NTS was significantly greater than in the rats with lesions that included the AP and a large amount of NTS. The enhanced saline intake does not appear to be related to a sodium deficit (7). Earlier studies found that sodium depletion produced by the same paradigm as in this study significantly increased 3% saline intake of the AP-lesioned and immediately adjacent NTS-lesioned rats and unlesioned rats above their baseline levels (7). In the present study, we failed to confirm this observation; Sx and Bx animals did not increase their

![Fig. 10. Almond-flavored sweetened condensed milk intake 72 h after a conditioning trial with paraquat expressed as percentage of conditioning trial intake. Both Sx (n = 14) and Bx (n = 12) rats consumed more milk during retention trial than during conditioning trial. CT (n = 16) showed suppressed intake during retention trial.](image)

**Table 2. Analysis of mean arterial blood pressure and heart rate**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Data</th>
<th>Maximal Changes With Phenylephrine</th>
<th>Baroreflex</th>
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<tr>
<td></td>
<td>MAP HR</td>
<td>MAP HR</td>
<td>Slope r Value</td>
</tr>
<tr>
<td>Sx (n = 8)</td>
<td>120.1 ± 1.5 387.3 ± 7.4</td>
<td>34.6 ± 2.5 -74.9 ± 10.9</td>
<td>-1.94 ± 0.28 0.74 ± 0.06*</td>
</tr>
<tr>
<td>Bx (n = 9)</td>
<td>115.7 ± 2.3 391.7 ± 11.2</td>
<td>29.9 ± 4.2 -56.1 ± 10.2</td>
<td>-1.68 ± 0.42 0.83 ± 0.07</td>
</tr>
<tr>
<td>CT (n = 13)</td>
<td>117.9 ± 3.3 406.5 ± 9.1</td>
<td>36.0 ± 4.1 -96.3 ± 10.6</td>
<td>-2.59 ± 0.36 0.91 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE. Phenylephrine was infused at 0–12 µg · kg⁻¹ · min⁻¹ iv. Sx, rats with complete lesion of area postrema (AP) and minimal damage to adjacent NTS; Bx, rats with complete lesion of AP with extensive damage to adjacent NTS; CT, rats with sham lesions; MAP, mean arterial blood pressure; HR, heart rate. *Significantly smaller than CT (P = 0.04).
intake. Moreover, the difference existing between animals with different lesion sizes when sodium intake was induced by sodium depletion was similar to that observed during ad libitum saline intake. In addition, there was a positive correlation between the amount of remaining NTS and the amount of spontaneous saline intake as well as saline intake after sodium depletion.

The mechanism underlying the enhanced intake of saline by rats with lesions of the AP remains unclear. It has been reported that central oxytocin can exert an inhibitory action on salt appetite (31). Thus it is possible that rats with lesions of the AP have a reduced release of oxytocin in the central nervous system or that the target site for central oxytocin is removed by the lesion. This possibility is supported by the reciprocal connections between the dorsomedial medulla and the parvocellular paraventricular nucleus that contains oxytocinergic neurons (1, 21, 30). A second possible mechanism by which lesions in the dorsomedial medulla might enhance sodium appetite is to interfere with signals from cardiopulmonary receptors reported to inhibit sodium appetite (16), much like the mechanism proposed to inhibit water intake above. Loss of input either humorally or neurally from these receptors would remove this inhibitory signal and result in an enhanced sodium appetite. It is also conceivable that the lesion interferes with gustatory input. This is not likely to be a direct effect of the lesion, because primary gustatory afferents terminate in the NTS millimeters rostral to the AP, but rather an effect of altering the integration of gustatory inputs in the hindbrain and causing an enhanced responsiveness to gustatory cues such as sodium.

Finally, preliminary behavioral studies suggest the LPBN is involved in the enhanced sodium appetite observed in rats with AP/mNTS lesions and may play a role in the ad libitum sodium appetite of rats with lesions of the AP (32). The LPBN in the pons receives a prominent projection from the AP and caudal two-thirds of the NTS (18, 20, 22, 30). In addition, the AP may have an important role in the modulation of the neural activity in the caudal NTS that also projects to the LPBN (30). It was observed in previous (4, 17), as well as present, studies that the sodium appetite of AP-lesioned animals decreased as lesions included more of the caudal NTS. Taken together, the above behavioral and anatomic evidence suggests that the balance between the input to LPBN from AP and from caudal NTS may be important in the regulation of sodium appetite.

An additional interesting observation from the present study is the effect of differential lesion size on body weight. Earlier studies reported that lesions centered on the AP resulted in significant decreases in body weight (3, 4, 9, 15, 34). Although lesioned rats began to gain weight 2 wk after surgery, their body weights never attained that of CT rats. In this experiment we only confirmed these observations but also demonstrated further that when the lesion included more of the adjacent NTS, the weight loss caused by lesions centered on the AP was attenuated. Moreover, our data indicate that this difference is apparent by the fourth postsurgical day. Differences in the size of lesions may cause rats to decrease their food intake or increase metabolic rate differentially. Studies in our laboratory indicate that the metabolic rate is not different between fully recovered lesioned and unlesioned animals (unpublished observations). However, the food intake, metabolic rate, and underlying neural and hormonal changes that occur during the initial period of weight loss remain to be elucidated.

Earlier studies also found that AP lesions cause exaggerated consumption of preferred foods, such as instant breakfast and chocolate chip cookies (9). In the study reported here, both lesioned groups ingested significantly greater amounts of another preferred food, sweetened condensed milk.

In summary, both rats with AP and small NTS lesions and rats with AP and large NTS lesions had significant body weight loss after surgery. However, as the lesion impinges more into the NTS, the level of body weight loss decreases. The amount of increased water intake produced by a challenge mimicking extracellular dehydration (Iso treatment) was significantly greater in rats with AP and large NTS lesions compared with rats with AP and small NTS lesions as well as the control group. On the other hand, 3-h ad libitum saline intake as well as saline intake after sodium depletion by rats with AP and small NTS lesions was greater than that of rats with AP and large NTS lesions. Both groups showed a significantly enhanced saline intake compared with intact control rats. These data suggest that the neural substrates involved in the control of water intake may differ from those that control saline intake. The neural population in the NTS bordering the AP may play a critical role in the control of water and saline intake and the regulation of body weight. Furthermore, inputs from the AP may be important in modulating the activity of this neural population to maintain proper fluid and energy balance.

Perspectives

Observations from these studies further implicate the AP and the NTS as important sites for the control of food and water intake. Most importantly, these studies reinforce the importance of a critical anatomic evaluation of lesions centered on the AP. Increasing damage to the adjacent NTS can result in remarkably different behaviors and lead to different conclusions.

How this region is involved in the control of fluid and energy balance is still unclear. Previous studies indicate that circulating ANG II acts in the forebrain to stimulate water and salt intake. It is likely that hindbrain projections to the forebrain influence these forebrain circuits to modulate fluid intake. In a model proposed by Lind and Johnson (19), increased synaptic norepinephrine (NE) in the median preoptic nucleus (MnPO) modulates the action of increased ANG II to facilitate neural output to higher-order brain areas involved in control of drinking behavior. The availability of NE in MnPO is proposed to be inversely proportional to the systemic blood pressure or blood volume.
(35). In lesioned rats NE release in the MnPO may be greater than NE release in intact rats. This would result in an increased behavioral response. Mechanisms to achieve a greater NE release could include a more pronounced hypotensive action of Iso in lesioned rats or the possibility that the lesion interferes with an afferent pathway that acts to suppress activity in hindbrain NE-containing neurons. The nature of this potential afferent pathway remains unclear. The AP is a circumventricular organ and lacks a blood-brain barrier. Thus large circulating substances can penetrate this region of the brain and directly influence neurons within the AP. Additionally, neural input from thoracic and abdominal viscera synapses in this region and the lesion could directly interfere with afferent fibers, such as those arising from low-pressure volume receptors.

Signals acting in the dorsomedial medulla to suppress fluid and salt intake are yet to be identified. Earlier studies have focused on input from the cardiovascular system. However, more recent studies indicate that input from the gastrointestinal tract is also important, particularly for the control of short-term intake of saline (5). Clearly, more research is necessary to elucidate the mechanisms utilized by the dorsomedial medulla to modulate fluid balance.

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REFERENCES


