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Disruption of Drinking to Intracranial Angiotensin by a Lateral Hypothalamic Lesion[1]

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BLACK, S. L., J. KUCHARCZYK AND G. J. MOGENSON. *Disruption of drinking to intracranial angiotensin by a lateral hypothalamic lesion.* PHARMAC. BIOCHEM. BEHAV. 2(4) 515–522, 1974. – Rats were repeatedly induced to drink by injecting angiotensin-II into either of two bilateral cannulae in the preoptic area. A unilateral lesion subsequently placed in the lateral hypothalamus sharply reduced the amount of water ingested by the rats in response to the preoptic injection of angiotensin ipsilateral to the lesion, and reduced drinking to a lesser extent to contralateral stimulation. Following the slow recovery of drinking in response to angiotensin, a second lesion of the lateral hypothalamus was produced on the contralateral side. This lesion again caused a sharp decrease in water intake to angiotensin, this time equally to contralateral and to ipsilateral stimulation. These results suggest that drinking elicited by the injection of angiotensin into the preoptic area depends primarily on an ipsilateral pathway from the preoptic area through the lateral hypothalamus. However, after recovery from the disruption produced by a unilateral lesion of the lateral hypothalamus, the drinking response also requires the participation of a crossed pathway from the preoptic area through the contralateral lateral hypothalamus.

Angiotensin Intracranial chemical injection Lateral hypothalamus Preoptic area Thirst

A RAT will quickly begin to drink following the microinjection of angiotensin-II into various forebrain structures [6]. These brain regions may therefore contain specialized receptors which initiate drinking when stimulated by angiotensin [7]. Since the preoptic area is one of the brain regions most sensitive to angiotensin for the elicitation of this response [6, 8, 27], it appears to be a primary site of these receptors. The question can then be asked: where do the signals from these receptors go? It is possible that the signals pass through the lateral hypothalamus (LH), a region of demonstrated importance in the control of drinking behavior. Bilateral lesions of the LH are known to abolish or delay drinking in response to cellular dehydration [25,28], plasma volume depletion [25,26], and ligation of the inferior vena cava [25], while unilateral as well as bilateral LH lesions disrupt drinking in response to the intracranial injection of carbachol [22,31]. These results indicate that the integrity of the LH is essential for the occurrence of various types of elicited drinking behavior. Similarly, the integrity of the LH may be necessary in order that drinking be elicited in response to the injection of angiotensin into the preoptic area. The experiment reported here supports this hypothesis by demonstrating that a unilateral lesion of the LH impairs drinking in response to an injection of this type.

METHOD

Animals and Surgical Procedures

Male Wistar rats weighing between 350 and 400 g at the time of surgery were used. They were housed in individual wire-mesh cages in a temperature-controlled room with a 12:12 light-dark cycle and maintained ad lib on a powdered high carbohydrate diet [24]. Water was available, in bottles with curved glass spouts open at the top to minimize spillage. Water intakes, food intakes, and body weights were determined at the same time every day.

Following one week of adaptation to the powdered diet, each rat was anaesthetized with sodium pentobarbital (Nembutal; 50 mg/kg), preceded by atropine sulphate (10 mg), and placed in a stereotaxic instrument for implantation of two cannulae and two electrodes. The cannulae, made from 23 ga disposable needles with insect pins inserted as obturators, were implanted bilaterally in the preoptic area, each 1.2 mm from the midline. The electrodes, consisting of size 00 insect pins coated with Epoxylite insula-

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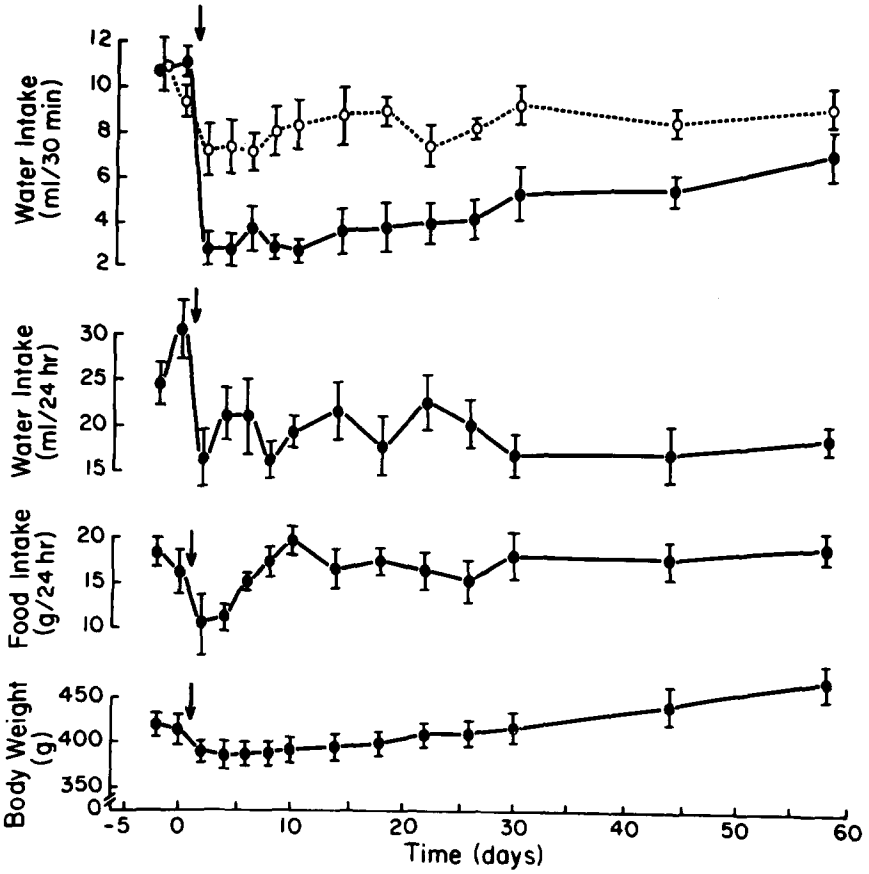

FIG. 1. The effect of a unilateral lesion of the lateral hypothalamus (n = 9) on drinking induced by the injection of angiotensin into the preoptic area, and on daily water intake, food intake, and body weight. The data plotted are mean values ± the standard error of the mean. In the uppermost panel the dotted line (open circles) refers to water intakes in response to angiotensin stimulation in the preoptic area contralateral to the lesions; the solid line (closed circles) refers to water intakes in response to ipsilateral stimulation. The lesion was placed on the day indicated by the arrow.

tion except for 0.5 mm at the tip, were inserted bilaterally into the lateral hypothalamus. The rats were allowed to recover for a minimum period of 10 days.

Experimental Procedure

The injected dose consisted of 500 ng of angiotensin-II (Hypertensin–CIBA) dissolved in 1 μl of water [6]. Water was chosen as the vehicle in order to ensure the hypotonicity of the solution and thus avoid possible stimulation of osmoreceptors. The dose was delivered through a microliter syringe attached to a 30 ga injector cannula previously filled with the solution. When inserted, the injector cannula extended 0.5 mm beyond the guide cannula implanted in the preoptic area of each rat. On each trial, the obturator was removed from one of the two guide cannulae and the injector cannula inserted for delivery of the 1 μl dose over a period of 5 sec. The obturator was immediately replaced and the rat returned to its cage. The water bottle was replaced by an inverted 15 ml graduated centrifuge tube with a glass spout, and water intake (±0.5 ml) was measured for the next 30 min. Food was not available to the rats during this test.

Angiotensin injections were given on alternate test trials into the left and right cannulae. Before placement of the first unilateral lesion in the LH a minimum of 6 daily trials was carried out (i.e., 3 per cannula). In some cases, further trials were given until the amount drunk was relatively constant from one trial to the next. The rat was then lightly anaesthetized with ether and a lesion produced by passing 3 mA anodal current for 15 sec through one of the electrodes implanted in the LH, with the indifferent electrode clipped to the ipsilateral ear. After placing the lesion, angiotensin trials were carried out daily for the next 10 days, and less frequently thereafter. The second lesion to the contralateral LH was made 2 months after placement of the first lesion, and angiotensin tests were continued according to the same procedure. At the end of this period, the rats were killed and their brains removed and prepared for histological analysis according to standard histological techniques.

The data were analyzed according to the Scheffé procedure, as modified for planned comparisons [4]. Comparisons were planned for the four day period before lesioning, the first 8 days after lesioning, the entire postlesion period, and for the final day of testing. This

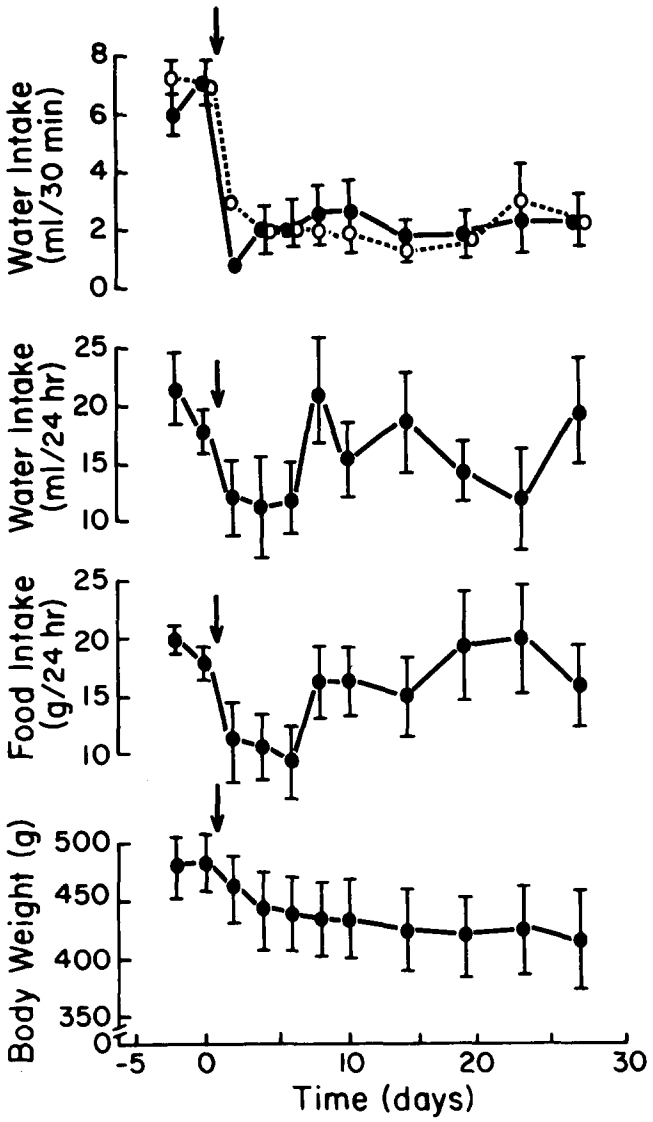

FIG. 2. The effect of a second lesion of the lateral hypothalamus (n = 6) contralateral to the first lesion on drinking induced by angiotensin, and on daily water intake, food intake, and body weight. The symbols are the same as in Fig. 1.

conservative method avoids the difficulties associated with multiple tests of significance by setting an overall experimentwise error rate for each group of comparisons rather than reporting the level of significance for each individual comparison. In the present experiment, the experimentwise error rate was set at 0.05; only comparisons significant beyond this value are specifically noted as significant in the results section.

RESULTS

The surgical procedure of implanting two cannulae into the preoptic area and two electrodes into the LH of each rat caused the animals to lose approximately 5% of their preoperative body weights in the immediate postoperative period. Their body weights soon began to recover, however, and were close to or above their preoperative values when testing with angiotensin began. Thus, the surgical procedure was not unduly stressful for the rats. Data are presented for 9 rats with both cannulae functional and in which unilateral lesions of the LH were made (Fig. 1). Six of these rats received a further lesion of the LH on the side contralateral to the first (Fig. 2). Data obtained from 5 additional rats were excluded from analysis because either the cannulae or lesions were outside the appropriate areas. The decision to exclude these rats was made without knowledge of the results obtained.

First LH Lesion

Placement of a unilateral lesion in the LH caused severe and prolonged attenuation of drinking in response to angiotensin injected into the preoptic area ipsilateral to the lesion. The water intakes elicited by angiotensin were significantly decreased in comparison with the intakes before placement of the lesions, both for the first 8 days and for the entire 2 month observation period after placement of the unilateral lesions. This decrease in elicited water intake was observed in every animal tested. Drinking in response to an injection on the side contralateral to the lesion was also significantly attenuated, both for the first 8 days after placement of the lesions and for the entire period of observation. However, the degree of disruption of drinking was different in the two cases. The water intakes elicited by angiotensin administration to either side of the brain did not differ significantly before placement of the unilateral lesions. Afterwards, the intakes in response to stimulation on the side ipsilateral to the lesion were significantly less than the intakes in response to stimulation on the contralateral side. This was true for both the first 8 days after placement of the unilateral lesions, and for the entire period of observation. Moreover, this differential effect of site of stimulation on drinking behavior was observed for each of the nine rats. Thus, the region of the lateral hypothalamus ipsilateral to the site of preoptic stimulation is of particular importance for the elicitation of drinking by angiotensin.

Although a unilateral lesion clearly disrupted drinking in response to angiotensin administered on the side ipsilateral to the lesion, slow recovery of this response occurred. For example, 14 days after placement of the lesions, 7 of the 9 rats were drinking less than 50% of their pre-lesion intakes when stimulated on the side ipsilateral to the lesion. However, 45 days later only one rat was still drinking less than 50% of its pre-lesion intake in response to angiotensin. At this point (2 months post-lesion) the intakes elicited by angiotensin injected on the side ipsilateral to the lesion did not differ significantly from the intakes elicited by stimulation on the contralateral side. With regard to pre- and post-lesion comparisons, the intakes elicited by stimulation on the side contralateral to the lesion on the final day of testing did not differ significantly from the intakes observed in response to stimulation before placement of the lesions. However, the intakes to stimulation on the ipsilateral side were still significantly lower than during the pre-lesion period. Therefore, recovery of drinking in response to stimulation by angiotensin on the side ipsilateral to the lesion was not quite complete two months following placement of the lesion.

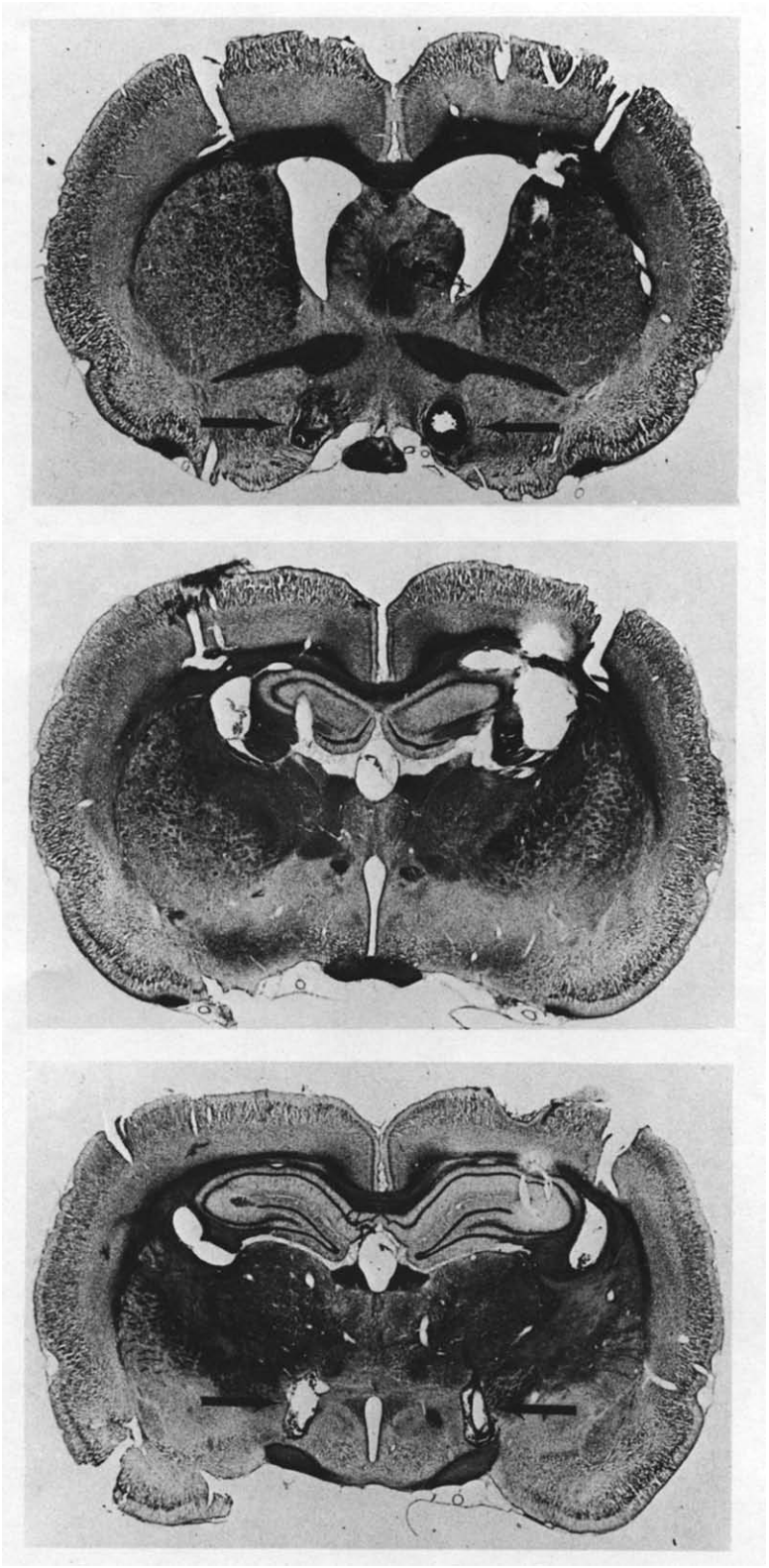

FIG. 3. Photomicrographs of coronal brain sections showing (a) cannulae placements in the preoptic region (arrows), (b) intact brain between the injection and lesion sites and (c) lesions in the lateral hypothalamus (arrows) for a representative animal.

As expected, the unilateral lesions of the LH also caused changes in ingestive behavior and in regulation of body weight. Daily (24 hr) water intakes were significantly reduced during the first eight day period following placement of the lesions, for the entire two month observation period, and on the final day. Significant changes in food intake were not observed for these periods, although the data suggest a transient decrease during the first four days after placement of the lesions. The body weights of the rats declined significantly during the first eight days after placement of the unilateral lesions in comparison with their body weights before placement of the lesions. This effect of the lesions did not persist, and the rats eventually began to gain weight. On the final day of observation, the body weights of the rats were significantly greater than during the pre-lesion period.

Second LH Lesion

The water intakes elicited by angiotensin injected on either side of the brain declined sharply following placement of the second LH lesions. This time, however, the post-lesion drinking in response to stimulation on one side of the brain did not differ significantly from the post-lesion drinking to stimulation on the opposite side. In comparison with the pre-lesion intakes, the post-lesion intakes were significantly lower for the first 8 days after placement of the second lesion, for the entire 26 day period of observation, and on the final day of observation. Observations beyond this 26 day period are not reported because one of the 6 rats, which was adipsic and aphagic, died. However, 5 of the remaining rats showed only limited recovery of drinking in response to angiotensin during an additional one month period of observation.

Daily water intakes during the post-lesion period were not significantly different from those before placement of the lesions, either in the first 8 days after placement of the lesions, or during the entire 26 day period of observation. However, the second lesion caused some alteration of regulation of food intake and body weight. Food intakes were significantly decreased during the first 8 days after placement of the lesions, but were not significantly different from pre-lesion values when compared over the entire 26 day period of observation. Body weights declined slowly throughout the post-lesion period. These weights were significantly lower than in the pre-lesion baseline period: for the first 8 days after placement of the lesions, for the entire period, and on the final day. However, only one of the 6 rats required tube feeding because its intake of food and water was insufficient to maintain its body weight.

Histological Analysis

Photomicrographs of a representative set of cannulae and lesion placements are presented in Fig. 3. The two cannulae implanted in each rat extended through the lateral ventricles into the preoptic region of the brain. In a number of cases, the lateral ventricles were enlarged, probably as a result of interference with the circulation of cerebrospinal fluid. The cannulae tips were located within the preoptic area, and were placed symmetrically about the midline on the border of the medial and lateral preoptic areas. In 5 rats, the cannulae tips were at the level of the suprachiasmatic nuclei. In the remaining 4 rats, the tips were localized somewhat anterior to this level (approximately where the anterior commissure first crosses the midline). In 2 of the latter rats, the tips were more dorsal than for the other placements, ending at approximately the level of the anterior commissure.

The lesions of the lateral hypothalamus extended in a posterior direction from a point just behind the cannulae tips but, as demonstrated by Fig. 3, clearly separate from the cannulae tips in all but one rat. The lesions reached their maximum size at the level of the anterior edge of the ventromedial nucleus and, in most cases, ended at the point where the ventromedial nuclei were at their widest extent. The lesions included damage to the medial forebrain bundle, particularly the part adjacent to the internal capsule, and extended slightly into the internal capsule. The anterior part of the zona incerta received moderate damage in approximately half the cases. Restricted bilateral damage to the hippocampus and thalamus was also observed, a consequence of the passage of the chronically implanted electrodes into the hypothalamus. In general, the region of destruction common to all the lesions was the anterior part of the lateral hypothalamus, and the lesions were within the "critical area" described by Gold [13]. It should be recognized, however, that because the animals were allowed to survive for 2–3 months after placement of the lesions, localization of the damage caused is necessarily approximate, in this study as in any, where prolonged survival after placement of a lesion is required [30].

DISCUSSION

The research presented here includes two major findings: (a) unilateral and bilateral lesions of the lateral hypothalamus severely attenuate drinking in response to the injection of angiotensin into the preoptic area: and (b) recovery from the disruption of elicited drinking is possible, at least for the case of a unilateral lesion. These results have now been replicated in a subsequent study in which smaller lesions were placed more caudally in the lateral hypothalamus [16]; there was, therefore, a larger amount of tissue between the cannula and the lesion.

The findings have a number of implications. Previous work has established the LH as the possible site of receptors which cause drinking when stimulated by angiotensin at relatively high dose levels [6]. The present results demonstrate the essential role of the LH as an intermediary between the highly sensitive receptors of the preoptic area and the organized response of drinking. This conclusion is consistent with the observation [25] that bilateral lesions of the LH impair the elicited drinking of rats to ligation of the inferior vena cava, an effective stimulus for increasing the circulating levels of angiotensin. Secondly, the results reported here suggest that the neural circuit for angiotensin induced drinking passes through the LH primarily on the side ipsilateral to the site of preoptic stimulation. This follows from the observation of major ipsilateral and minor contralateral attenuation of drinking following the placement of a unilateral lesion of the LH. If the reduced drinking in response to stimulation was instead attributable to lessened motivation to respond as a result of the lesions, the decrement in response should have been as severe on the side contralateral to the lesion, but it was not. The same observation rules out the possibility that the deficit in response was due to general debilitation of the rats rather than to specific interference with drinking behavior.

Note that the deficit in drinking response to angiotensin

did not depend upon the presence of aphagia and adipsia. This observation further argues against an interpretation of this experiment in terms of a non-specific motor deficit, and suggests that drinking in response to angiotensin may be independent of other mechanisms for regulation of food and water intake. In fact, the disruption of daily food and water intakes in this experiment was not severe. This result suggests that the lesions may not have been in an area critical for regulation of daily food and water intake, although this conclusion does not take into account the fact that the lesions were placed in two stages, with a considerable time period between each ablation. The behavioral effects of such two-stage lesions are always less than that of bilateral lesions placed simultaneously [14,29]. In any case, the rationale of this experiment does not require the occurrence of adipsia and aphagia – only that the lesions are effective in disrupting drinking in response to angiotensin.

The identity of the ipsilateral pathway which these results suggest passes from the preoptic receptors through the lateral hypothalamus is unknown. The cannulae placements are such that angiotensin infused through them can stimulate both lateral and medial preoptic areas. Although the medial preoptic area is more sensitive for elicitation of drinking in response to angiotensin [8], it has no known direct connections with the lateral hypothalamus. However, the medial forebrain bundle sends fibres through the lateral preoptic area which descend through the part of the lateral hypothalamus destroyed in the present study. This pathway may also have direct connections with medial areas [19] and, may therefore, receive inputs from both medial and lateral preoptic areas before reaching the LH. This proposal is supported by the results of recent electrophysiological experiments in which it was observed that neurons in the lateral hypothalamus are activated by angiotensin microinjected into the preoptic region [3,17]. On the other hand, on the basis of evidence relating to behavioral changes after lesions, a pathway from the medial and lateral preoptic areas which passes through the anterior hypothalamus to the lateral hypothalamus has been proposed [23]. The placement of the LH lesions in the present study also suggests that fibres of the nigrostriatal bundle may have been destroyed [20]. This observation is of interest in view of the proposal [9] that angiotensin-induced drinking depends on a central catecholaminergic mechanism. However, the nigrostriatal bundle is an ascending pathway; a descending pathway of this kind from the preoptic area has not yet been demonstrated.

The observation of recovery of drinking behavior in response to angiotensin following disruption by a unilateral lesion is of particular interest. This finding is analogous to the recovery of food and water intake observed after bilateral lesions of the LH [28]. Recently, it has been reported that recovery in the latter case may be accelerated by various procedures, including pre-lesion experience [5,10], pretreatment with α-methyl-p-tyrosine [12], with nerve growth factor [2], and by prior destruction of the frontal cortex [11]. One explanation of these findings is that the recovery process is mediated by denervation supersensitivity [12]. This hypothesis provides one explanation of the recovery of function observed in the present study. Alternatively, the observed recovery may be due to the post-lesion growth of axons which result in new functional connections [18].

Whatever the cause, it appears that the return of drinking in response to the intracranial injection of angiotensin is mediated, at least in part, by fibres which cross the midline. This conclusion follows from the observation that the placement of the second LH lesion, on the side contralateral to the first, reinstituted the disruption of drinking, not only to angiotensin stimulation on the same side as the second lesion, but also on the opposite, recovered side of the brain.

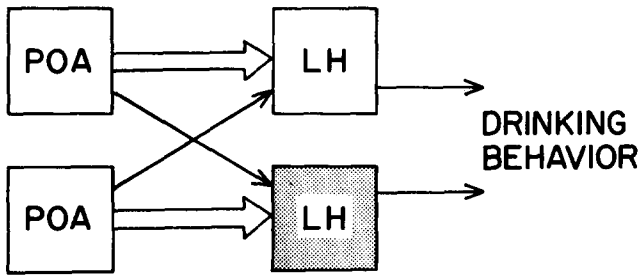

FIG. 4. Model of the functional connections between the preoptic area (POA) and the lateral hypothalamus (LH) which may mediate the drinking response to angiotensin injected into the preoptic area. The crosshatched area represents a lesion.

A model which accounts for these results is presented in Fig. 4. According to the model, the presumed receptors for angiotensin in the preoptic area connect primarily with the LH on the ipsilateral side; the model also assumes a component of lesser importance which crosses the midline before reaching the LH. After interruption of the ipsilateral pathway within the LH, angiotensin injections into the preoptic area on this side are unable to sufficiently activate the LH through the remaining crossed pathway. Injections on the undamaged side remain effective because the ipsilateral pathway on that side is intact. The recovery of function which follows may be mediated in one of two ways: (1) by an increase in the number of synaptic connections the crossed pathway makes with the LH on the side contralateral to the side receiving a lesion or (2) by recovery of function on the same side as the site of the lesion through denervation supersensitivity or axonal regrowth. However, whether the recovery occurs on the side ipsilateral or contralateral to the lesion, it will now critically depend on the additional input to the LH provided through the crossed pathway. As a result, the second lesion, placed on the side contralateral to the first, will include destruction of not only the ipsilateral pathway on that side, but also the termination of the crossed pathway on which the recovery of function depends. Therefore, the second lesion will disrupt drinking to stimulation on either side of the brain.

This model provides a useful interpretation of the observations reported in this study. However, the model is not consistent with the recent proposal of Simpson and Routtenberg [21] that drinking in response to angiotensin injected into the preoptic area depends on stimulation of the subfornical organ. These authors suggest that when angiotensin is injected into the preoptic area, it rapidly diffuses into the ventricles or into capillaries within the preoptic area. The angiotensin is then carried to the subfornical organ, the site of primary thirst receptors for this substance. Simpson and Routtenberg point out that the

subfornical organ is a region of weakness of the blood-brain barrier, and thus angiotensin may readily enter this structure from the blood. However, they do not indicate how angiotensin may circumvent the blood-brain barrier when leaving the capillary network which perfuses the subfornical organ. Their alternate suggestion of diffusion through the ventricles avoids this difficulty. This version of the hypothesis is supported by evidence that labelled angiotensin injected into the preoptic area does enter the ventricles [15]. However, it has recently been demonstrated that drinking is elicited with low doses (1.25 ng) of angiotensin using a small volume (0.1 μl) [27] which is evidence against the diffusion hypothesis. Furthermore, since the subfornical organ is a midline structure, the diffusion hypothesis suggests that the unilateral destruction of the lateral hypothalamus should either attenuate drinking to preoptic injections of angiotensin given on either side of the brain, or not at all. Instead, as observed in this study, the attenuation is greater to stimulation on the side ipsilateral to the site of the lesion. This finding, of course, does not suggest that the angiotensin-sensitive receptors cannot be located close to the walls of the third ventricle [1]. However, it does suggest that the receptors are unlikely to be located primarily in a midline structure such as the subfornical organ. Nevertheless, Simpson and Routtenberg [21] have reported that destruction of the subfornical organ impairs drinking elicited by the injection of angiotensin into the preoptic area. How can this intriguing finding be incorporated in the model proposed above? One way, perhaps, is to assume that the LH receives inputs from both the subfornical organ and from the preoptic area, and requires the participation of both pathways in order that a drinking response can be elicited. The crossed pathway of the model proposed here may, in fact, be due to the diffusion of angiotensin into the subfornical organ from the preoptic area. However, it is clear from the present results that the subfornical organ cannot be the only structure of importance in mediating drinking induced by the preoptic injection of angiotensin. This response also depends, at least initially, on the integrity of a unilateral pathway through the LH.

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