Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 2532–2537, March 1999
Physiology

Correlation of regional cerebral blood flow and change of plasma sodium concentration during genesis and satiation of thirst

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Contributed by Derek Denton, December 21, 1998

ABSTRACT **Positron emission tomography studies were conducted during genesis of moderate thirst by rapid i.v. infusion of hypertonic saline (0.51 M) and after satiation of thirst by drinking water. The correlation of regional cerebral blood flow with the change in the plasma Na concentration showed a significant group of cerebral activations in the anterior cingulate region and also a site in the middle temporal gyrus and in the periaqueductal gray. Strongest deactivations occurred in the parahippocampal and frontal gyri. The data are consistent with an important role of the anterior cingulate in the genesis of thirst.**

Osmoregulation is a physiological function crucial for survival. Vertebrates can modify serum osmolality by regulating fluid intake (i.e., drinking) and urinary excretion. For an animal to increase fluid intake (i.e., to decrease serum osmolality), it must experience a sensation motivating it to find and drink water. This sensation is thirst.

The major biological determinate of the subjective experience of thirst is serum osmolality. Cellular dehydration is an effective stimulus to increase drinking in all vertebrate species that show drinking behavior (1–3). For example, when a sea-water eel is transferred to fresh water, it ceases to drink, but it can be made to drink again by infusing hypertonic NaCl i.v., by bleeding, or by injecting angiotensin systemically (4). An increase in plasma osmolality of 1–2% causes mammals to drink (1, 3). A decrease of extracellular fluid volume also initiates drinking but is less dominant in the hierarchy of motivations to drink. A decrease of blood volume or pressure of about 10% or more is required to arouse thirst (2). This change also entrains a delayed increase of Na appetite.

In mammals, the thirst of cellular dehydration can be aroused by water deprivation, injection of hyperosmotic solutes that do not enter cells, or potassium deficiency. Water deprivation, the selection pressure relevant in nature, is mimicked by systemic or ICV infusion of hypertonic solutions, but it is noteworthy that such procedures do not produce the concurrent reduction of extracellular fluid volume that occurs with water deprivation.

Changes other than osmolality are also experienced as thirst. For example, when the mouth becomes dry from prolonged speech or from breathing dry air, this is experienced as thirst and is assuaged by drinking. In the history of analysis of thirst, Cannon's theory (5) that dry mouth was the sole determinant of thirst and water-seeking behavior was influential for many years. Cannon's theory, however, was superseded when physiological data made clear the dominance of hypothalamic neural genesis of thirst. Anteceding Cannon, Claude Bernard (6) showed in animals with esophageal (horse) and gastric (dog) fistulae that drinking would continue to the point of exhaustion, despite the wetness of the oral mucosa. Nevertheless, a dry mouth is subjectively experienced as thirst (i.e., does lead to drinking) and must be controlled in the course of an experiment directed at the brain mechanisms of osmoregulation, as is reported here.

The present evidence is that the genesis of thirst is subserved by osmoreceptors in the circumventricular organs of the anterior third ventricle, which respond to a change of osmotic pressure in the plasma, and also by [Na] sensors in the anterior wall of the third ventricle, which respond to a change in cerebrospinal fluid and brain extracellular fluid [Na] (7–10). A lesion of the anterior wall of the third ventricle involving organum vasculosum of the lamina terminalis, median preoptic nucleus, and subfornical organ causes permanent or transient adipsia (11). Thirst occurring as a result of extracellular volume depletion has been shown in some species to be caused by an increase of angiotensin II in peripheral plasma acting on circumventricular organs and also by neural inflow from stretch receptors in the great vessels and the atria of the heart (3). The role of intracerebral angiotensin II in the genesis of thirst may be that of a cotransmitter. For example, thirst evoked by intracerebral infusion of hypertonic NaCl in rats, sheep, cattle, rabbits, and mice is inhibited by concurrent intracerebral infusion of the angiotensin AT_1 receptor antagonist losartan (12).

An animal, when dehydrated, will drink rapidly to satiation over 3–10 min. The satiation process is caused by oral, pharangoesophageal, and gastric neural inflow (13). Although there is variation among species as to whether immediate correction of total deficit occurs, the amount drunk is rather precisely that needed to correct serum osmolality. However, the water will not be absorbed from the gut or serum osmolality will not be corrected until long after drinking has ceased. Similarly, in humans, the subjective experience of thirst is eliminated by drinking to satiation long before osmolality is corrected (see *Results*). Thus, to identify brain areas specifically engaged in osmoregulation, drinking to satiation contrived a dissociation between thirst and plasma osmolality.

In view of the preceding considerations, a positron emission tomography (PET) blood-flow, brain-activation study was performed to identify brain regions sensitive to changes of plasma [Na], as distinguished from those sensitive to nonosmolar components of the sensation of thirst. This was done by imaging subjects serially as they were brought from a normal osmolar, nonthirsty state to a hyperosmolar, thirsty state. To remove the nonosmolar components of the experience of thirst, subjects were allowed to wet their mouths and, thereafter, to drink to satiation. Imaging was performed at each of these stages. Neither of the latter two interventions (wetting the mouth and drinking) altered plasma Na or serum osmo-

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Abbreviation: PET, positron emission tomography.

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lality. The brain areas selectively sensitive to changes of plasma [Na] were identified by creating statistical parametric images of the correlation (r images) between change of plasma [Na] and regional cerebral blood flow across all of the previously described conditions.

EXPERIMENTAL METHODS

Subject Selection and Preparation. All subjects were normal, right-handed, nonsmoking male volunteers between the ages of 24 and 36 years. Informed consent was obtained from each subject; the forms were approved for this study by the Human Subjects Institutional Review Board and the Radioisotopes Committee at the University of Texas Health Sciences Center, San Antonio. Each subject was instructed to refrain from alcohol ingestion for 24 h before the study but otherwise to have normal fluid intake. On the morning of study, the protocol was reviewed with each subject and instructions were given with regard to the assessment of thirst and dry mouth sensation during the study. The subjects were asked to be prepared to rate thirst and dry mouth on a scale of 0 to 10, with 10 being the most thirst or dry mouth the subject had ever experienced and 0 being no sensation of thirst or dry mouth. After receiving these instructions, each subject emptied his bladder and had a physical examination before being placed in the tomograph. i.v. cannulae were inserted into each forearm, on the left for blood sampling and injection of the bolus of $H_2{}^{15}O$ for scanning and on the right side for rapid infusion of hypertonic saline.

Image Acquisition. PET and MRI scans were performed on each subject lying supine with his head supported in a foam-padded, hemicylindrical head holder, with eyes closed and in a quiet room. The methods used at the Research Imaging Center (RIC), University of Texas Health Science Center, have been described (14–17). PET and anatomical MRI of each subject were coregistered and spatially normalized with an affine, nine-parameter algorithm (17) (RIC, University of Texas Health Science Center at San Antonio). Images were normalized to the atlas of Talairach and Tournoux (17, 18) and referenced in millimeters relative to the anterior commissure. Statistical parametric images were computed (19), and local maxima were extracted (20) with previously validated algorithms (RIC, University of Texas Health Science Center at San Antonio). Each correlation coefficient was calculated as the correlation between the change in plasma [Na] per scan and the change in regional cerebral blood flow for each voxel per scan. Each correlation coefficient calculation included all of the scans for all of the subjects. The coefficients were histogrammed and observed to be normally distributed. The mean (μ) and standard deviation (σ) of the distribution were calculated, and the Z score per voxel was then calculated from $Z = (r - \mu)/\sigma$. Anatomical labels were applied automatically by using a three-dimensional electronic brain atlas (21), with Brodman areas referenced to that atlas.

Experimental Protocol. Previous studies of animal and human subjects have established that the sensation of thirst is generated if plasma osmolality increases by about 2% (1, 3). Based on previous studies of hypertonic NaCl infusion in human subjects (22–24), we estimated that a constant infusion of 3% NaCl at 0.2 ml·kg^{-1} per min for a period of 25 min (0.51 M NaCl at 11.5 ml·kg^{-1} per h for a period of 25 min = 167 mmol NaCl for a 70-kg subject) should produce the desired increase in plasma osmolality. This infusion effectively produced mild thirst and an increase of plasma osmotic pressure by 2% and was used in the first five of the 10 subjects. In another five subjects, we infused the NaCl at the same rate but for twice as long, giving 334 mmol of NaCl for a 70-kg subject. This produced moderate to severe thirst and increased plasma osmotic pressure by approximately 3%. After the PET scans were obtained in the control state, the constant infusion of 0.51 M NaCl (0.2 ml·kg^{-1} per min) for 25 or 50 min was commenced. PET measurements to assess the effects of increasing plasma [Na] and osmolality on brain activation were acquired at the midpoint and end of infusion. The subjects reported their sense of dry mouth and thirst at intervals during the infusion. They were imaged again when thirst had reached an apogee (as evidenced by two to four equivalent subjective reports over 10–20 min). At that time, the subjects, having been trained beforehand, irrigated their mouths without swallowing to remove the "dry mouth" component of thirst and were again imaged. The irrigation ameliorated some discomfort from a dry mouth but did not remove thirst. Within 5 min, the subjects were allowed to drink water to satiation and were imaged 3 min later and again 14, 45, and 60 min after drinking. Each subject had 10 scans (with the exception of one who did not have the 50% of infusion scan). Blood samples for measurement of plasma [Na] and osmolality were collected at the following times: immediately before the control scan, at the time of the midway scans, at the end of i.v. infusion of hypertonic NaCl, at the time of maximum thirst scan, at the time of the scan 3 min after drinking, and also before a 60-min posthydration PET scan.

RESULTS

In all subjects, plasma [Na] and plasma osmolality increased during the i.v. infusion: mean baseline [Na] = 140.4 ± 1.0 mmol/liter (mean ± SEM); mean maximum thirst [Na] = 144.6 ± 0.6 mmol/liter ($P < 0.001$ by paired t test); and baseline plasma osmolality = 282.2 ± 1.5 mosmol/kg and with maximum thirst = 289 ± 2.1 mosmol/kg ($P < 0.001$; Fig. 1).

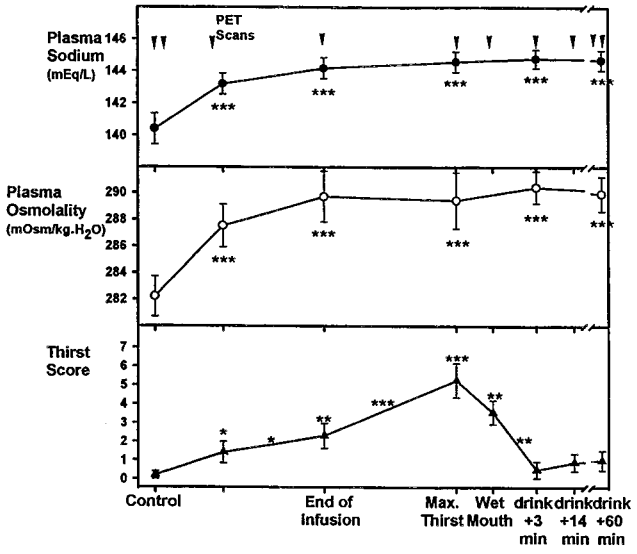

FIG. 1. Diagram of the effect on plasma [Na], plasma osmolality, and thirst score of 10 normal subjects as a result of the sequence of events in the experimental paradigm. After control estimations and baseline PET scans, a rapid i.v. infusion of 0.51 M NaCl was given. Blood specimens were taken and thirst scores were determined midway through and at the conclusion of infusion. Maximum thirst occurred a mean of 43 min later, when a blood specimen was collected and a PET scan was made. The subjects then irrigated their mouths with water. Five mintues later, a PET scan was made. Then the subjects were permitted to drink water to satiation. Blood was collected, and a PET scan was made 3 min after this. A PET scan was made 14, 45, and 60 min after drinking. A further blood specimen was collected for analysis 60 min after drinking. The data are presented as means ± SEM, and the PET scans are designated by arrows. Statistically significant changes are indicated by the asterisks. Asterisks placed above the observation points indicate a significant change from control observations. Asterisks placed between the observation points indicate a significant change between the two observations. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$.

Table 1. Correlation of regional cerebral blood flow and change of plasma [Na]

Hemisphere	Lobe	Gyrus or region	Brodman area	*x*	*y*	*z*	Cluster size, voxels	*Z* score
			Activations					
Limbic								
Left	Limbic	Cingulate	24	−13	−14	40	70	3.42
Left	Limbic	Anterior cingulate	32	−8	40	14	55	3.16
Left	Limbic	Cingulate	24	−7	−4	40	68	3.13
Left	Limbic	Anterior cingulate	32	−7	28	24	33	2.90
Parietal								
Right	Parietal	Posterior centrum	3/2/1	30	−22	42	12	2.93
Frontal								
Right	Frontal	Medial frontal	6	34	4	41	39	2.91
Temporal								
Right	Temporal	Middle temporal	39	42	−60	22	79	3.37
Left	Temporal	Middle temporal	21	−60	−36	−11	38	3.0
Right	Temporal	Superior temporal	38	38	18	−26	54	2.96
Right	Temporal	Superior temporal	22	40	−46	12	82	2.92
Occipital								
Right	Temporal	Middle temporal	37	37	−58	2	50	2.93
Cerebellum								
Right	Anterior	Culmen		14	−38	−8	23	3.11
Left	Posterior	Declive		−46	−69	−19	47	2.92
Left	Posterior	Declive		−51	−58	−20	45	2.91
			Deactivations					
Limbic								
Right	Limbic	Parahippocampal		22	−39	5	73	−3.61
Frontal								
Left	Frontal	Superior frontal	8	−18	18	48	33	−3.22
Left	Frontal	Middle frontal	6	−36	11	43	53	−3.21
Left	Frontal	Inferior frontal	44	−45	16	18	47	−3.16
Left	Frontal	Inferior frontal	47	−32	24	0	47	−2.97
Temporal								
Left	Temporal	Inferior temporal	38	−46	−46	−10	40	−3.06
Right	Temporal	Superior temporal	38	40	10	−18	78	−2.94
Other regions								
Right	Sublobar	Caudate		24	−38	14	110	−3.74
Right		Thalamus		2	−20	4	36	−2.95
								−2.98
Right	Thalamus	Pulvinar		18	−28	15	64	

Positive correlations (activations) and negative correlations (deactivations) of regional cerebral blood flow with change of plasma [Na]. *Z* scores of magnitude >2.90 or <−2.90 are recorded. Each voxel has a volume of 8 mm^3.

The plasma [Na] and osmolality did not change after the subjects wet their mouths or for 60 min after drinking to satiation.

When hypertonic saline was infused, all subjects became thirsty, but there was individual variation in degree, with those receiving the larger amount of hypertonic saline tending to have the greatest thirst.

With maximum thirst, the subjective rating on the scale 0–10 was 5.25 ± 0.9 (mean ± SEM) and 5.05 ± 0.8 for dry mouth sensation, both of which were significantly different from the baseline score (Fig. 1). The maximum thirst scan was made 43 ± 2.5 min (mean ± SEM) after completion of the i.v. infusion of hypertonic saline. Irrigating the mouth with water caused the dry mouth sensation, which had increased commensurately with thirst, to decrease to near the baseline level and also caused some reduction of the thirst sensation, although it was still significantly increased ($P < 0.01$) above baseline (Fig. 1). After drinking to satiation, the subjects' thirst sensation essentially disappeared and was near baseline 3, 14, 45, and 60 min after drinking.

The major brain activations that correlated with the change of [Na] relative to baseline are shown in Table 1. Four areas were left-sided in the left anterior and midcingulate areas (Brodmann 24 and 32; Fig. 2). Three of these activations represented the strongest of the four major effects caused by the change in plasma [Na] ($Z = 3.42, 3.16, 3.13$). All of these cingulate activations were within 13 mm of the midline, as were two other lesser left cingulate activations ($Z = 2.69, 2.76$). Two of the other strong activations ($Z \geq 3.0$; Table 1) occurred bilaterally in the middle temporal gyrus and in the culmen of the right cerebellum. The largest activation in the midbrain ($x = -6, y = -27, z = -3$; $Z = 2.82$) was in the region of the periaqueductal gray (Fig. 2), and three other sites of interest, although of lesser strength, were in the ventral pons and in the brainstem in the region of the medullary reticular formation ($Z = 2.50, 2.46, 2.46$; Fig. 2).

The strongest deactivations were in the right hippocampus ($Z = -3.61$) and immediately superior to it in the tail region of the caudate nucleus. Strong deactivations occurred also in sites in the superior, middle, and inferior frontal gyri and the inferior temporal gyrus (Table 1). In relation to the role of the diencephalic sensors in monitoring the internal milieu, a deactivation site in the hypothalamus was of interest. It was in the periventricular anterior hypothalamic region ($x = 4, y = -2, z = -8$). Another deactivation ($x = 2, y = -20, z = 4$) was in the posterior portion of the dorsomedial thalamic nucleus.

DISCUSSION

The infusion of hypertonic saline (0.51 M) at a rate and in amounts consistent with earlier studies of genesis of thirst and antidiuretic hormone release produced a highly significant

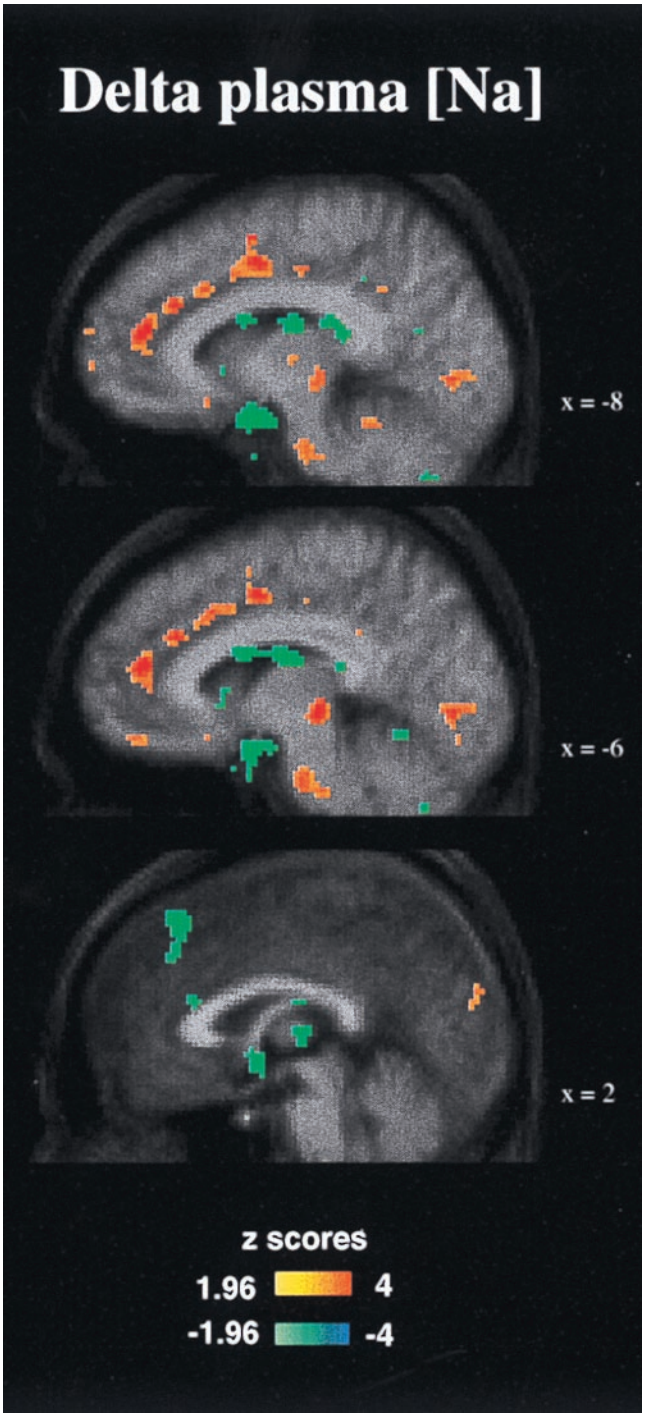

FIG. 2. The correlation of regional cerebral blood flow and the change in plasma [Na] derived from 99 PET scans from 10 subjects after the experimental sequence described in Fig. 1. In these saggital sections, a minus sign designates the left side, a plus sign designates the right side, and numbers indicate distance in millimeters from the midline. The sections are at $x = -8$, $x = -6$, and $x = +2$ and show activations (red-yellow) and deactivations (blue-green). The color coding of Z scores is shown in the figure. The anterior cingulate activations on the left side are evident.

increase in [Na] and osmolality of the plasma. Moderate thirst was produced. The plasma [Na] increased during the infusion and reached a plateau between the end of the infusion and the point of maximum thirst, which was 43 ± 2.5 min (mean ± SEM) later. Plasma [Na] did not decrease after the subjects wet their mouths or during the 60 min after drinking water to satiate thirst. Thus, the correlation of the change in plasma Na and the 10 PET scans from initial rest condition to the final images reflects the regional cerebral blood flow changes attributable to the increase of plasma [Na].

The strongest positive correlations implying greatest neural activity were in the left anterior and middle cingulate gyrus (Brodman areas 32 and 24) and accounted for three of the four major cerebral effects. Two lesser activations were also in the left cingulate. It is well established that the cingulate is the neocortical receiving area for input from phylogenetically more primitive neural regions of the brain. According to Vogt (25), as many as 20 thalamic nuclei project to different parts of the cingulate cortex with the anteromedial nucleus having the most diffuse projections throughout this region. Papez (26) noted that the limbic lobe contained the only telencephalic cortex with strong hypothalamic connections. The cingulate cortex has been directly implicated in reinforcement processes. Apart from the medial forebrain bundle, it has been shown that cingulate sites (e.g., Brodman areas 24, 25, and 32) also support self-stimulation, as do other sites in the limbic system, but self-stimulation has not been seen in any other cortical region (27). The cingulate cortex is critically involved in motor function, having more extensive projections to caudate and putamen than does any other cortical area. Layer V of the cingulate has neurons that project to caudate, putamen, pons, and periaqueductal gray. The output of layer V to motor areas under neocortical and hippocampal memory-based inputs may coordinate motor outputs associated with appetitive rewards (28).

Robinson and Mishkin (29) reported that electrical stimulation of the anterior cingulate in conscious monkeys caused water-drinking behavior simulating natural drinking, in that after 2 to 8 s the animals unhurriedly turned to water and drank in a natural fashion, suggesting the possibility that thirst had been evoked. These observations were made in the course of an extensive study in which 5,885 sites were stimulated in the brain of 15 monkeys, and alimentary responses involving feeding, water intake, food ejection, and vomiting were examined. The data supported the separate anatomical organization of control of water intake and food. Particularly well documented was the relationship between the anterior cingulate region, gyrus rectus, and subcallosal gyrus and water intake. It was noted that with water drinking there was a tendency of the animal to be "glued" to the water spout and to drink continuously while simultaneously responding to environmental distractions by movements of eyes, hands, and body. At times, unusual amounts of water were drunk by animals weighing 4–5 kg (e.g., 400 ml in 10 min). Other sites that evoked water intake included putamen, lateral, dorsal, and posterior hypothalamus, tegmentum, substantia nigra, and medial hypothalamus. A body of observations also involved water intake that followed only after stimulation. This stimulus-bound water drinking would start 2–5 min after stimulation, and 45 of the 48 sites where this happened were in the anterior cingulate, gyrus rectus, and subcallosal gyrus. Whereas the authors noted the difficulties of deducing a precise functional role for a region based on electrical stimulation or lesion and stressed the need of recording by other means the intact structure when functioning normally, the imaging data reported here could be consistent with the anterior cingulate activations being a component in a complex pattern of activations and deactivations subserving arousal of thirst as a result of increasing plasma [Na] and osmotic pressure. On this issue of a distributed system, the fact of clear initiation of drinking by cingulate stimulation contrasts with the observation of Coghill *et al.* (30) that a distributed pain system would explain the difficulty of eliciting painful sensations by cortical stimulation, because simultaneous action of several regions could be a necessary condition for pain and explain why discrete cortical lesions seldom lead to a complete reduction of pain.

The afferent and efferent connections of the anterior cingulate region include projections from the mediodorsal thalamic nuclei and also amygdala (25). A direct pathway has been demonstrated from the anterior cingulate to the periqueductal gray (31), which, in the experiments here, had an activation site, as noted below. Cholinergic neurons, including those originating in pontine nuclei, which were an activation site here, are a source of ascending brain stem efferents, which project to the thalamus in the monkey (32) and findings based on axonal transport of tracers show that cingulothalamic connections are reciprocal and widespread. Similarly, the anterior cingulate has rich reciprocal connections to the temporal pole and the frontal lobe (33, 34). In relation to the activations and deactivations in what has been termed the limbic association cortex involving the temporal and frontal lobes with the cingulate (35), Roland (34) noted the temporal pole along with the amygdala is clearly involved in emotional changes. In general terms, Vogt stated that surprisingly little is known about the contribution of individual or structural aggregates of neurons to functions of the cingulate cortex, and this incomplete understanding remains one of the principle challenges for the next decade of research into this area of the brain (25).

The activation identified in the periaqueductal gray region of the midbrain ($x = -6, y = -27, z = -3$; cluster size 33; $Z = 2.82$) was adjacent to the midbrain reticular formation areas identified by Roland's group, as involved in arousal and vigilance (36). The midbrain reticular sites discovered by Roland's group were activated by visual and sensory arousal, respectively, and were associated with activation of the intralaminar thalamic neurons. It was shown in our thirst study that a correlation of the change in plasma [Na] during the phase of increasing plasma [Na] (i.e., rest scan, 50% of infusion end of infusion, maximum thirst) showed that this midbrain reticular activation was the second strongest recorded ($x = -6$, $y = -26$, $z = -5$; cluster size 50; $Z = 4.06$). It is possible that this may reflect arousal contemporaneous with the increasing plasma [Na] generating thirst, parallel to Roland's suggestion of transition from relaxed wakefulness to high attention.

The induction of adipsia by lesions in the anterior wall of the third ventricle, as well as *cfos,* and electrophysiological studies indicate this region to be the locale of the osmoreceptors and [Na] sensors (11, 37). However, no strong activation was detected in this region correlating with the change of plasma [Na]. It is likely that the small circumventricular structures may be below the detection capacities of the PET methods used here, although a small activation was detected posteriorly in the mammillary bodies in scans during the phase of increasing [Na]. The physiological explanation for the deactivation in the periventricular anterior hypothalamus is not clear, as with other sites of deactivation, both diencephalic and cortical, which are established to have cingulate connections.

There is evidence that input to higher brain structures from subcortical and limbic systems associated with emotion is lateralized even in lower animals. Important fiber systems associated with motivation and emotion such as the medial forebrain bundle are right lateralized, and right hemisphere damage caused decreased emotionality (38, 39). The role of the right cerebral hemisphere in attentional processes, regardless of the modality or laterality of sensory input (40), and in alerting/vigilance (41) has also been reported. The cingulate activations reported here were left sided, but whether any tendency to laterality will emerge with the basic vegetative systems awaits further investigations.

We appreciate helpful discussion with Professor Frederick Mendelsohn. This work was supported by the Robert J. Jnr and Helen C. Kleberg Foundation, G. Harold and Leila Y. Mathers Charitable Foundation, The Howard Florey Biomedical Foundation of the U.S, the National Health and Medical Research Council of Australia [National Health and Medical Research Council (Australia) Block Grant 983001].

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