SEMINARS IN NEPHROLOGY

Water Intake and the Neural Correlates of the Consciousness of Thirst

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Thirst and resultant water drinking can arise in response to deficits in both the intracellular and extracellular fluid compartments. Inhibitory influences mediating the satiation of thirst also are necessary to prevent overhydration. The brain regions that underpin the generation or inhibition of thirst in these circumstances can be categorized as sensory, integrative, or cortical effector sites. The anterior cingulate cortex and insula are activated in thirsty human beings as shown by functional brain-imaging techniques. It is postulated that these sites may be cortical effector regions for thirst. A major sensory site for generating thirst is the lamina terminalis in the forebrain. Osmoreceptors within the organum vasculosum of the lamina terminalis and subfornical organ detect systemic hypertonicity. The subfornical organ mediates the dipsogenic actions of circulating angiotensin II and relaxin. Major integrative sites are the nucleus of the tractus solitarius, the lateral parabrachial nucleus, the midbrain raphé nuclei, the median preoptic nucleus, and the septum. Despite these advances, most of the neural pathways and neurochemical mechanisms subserving the genesis of thirst remain to be elucidated.
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The intake of fluids is an essential behavior for nearly all mammals, including human beings. If fluid intake does not occur regularly, dehydration will ensue regardless of the powerful urinary concentrating effect that vasopressin exerts on the kidney to reduce further fluid loss to a minimum. Much of our normal intake of fluid is of either a social or habitual nature, and often is associated with the ingestion of food, yet the brain mechanisms that initiate habitual drinking or that associated with meals still largely are unknown.[1]

Thirst and fluid intake as a response to body fluid deficit, however, has been investigated in some detail. Considerable knowledge has accrued during the past half century in regard to some of the brain regions and neural circuits that participate in the physiologic regulation of fluid intake when animals become depleted of body fluids. This fluid depletion may occur from either or both of the intracellular and extracellular compartments. Such homeostatic regulation of fluid intake is controlled by the thirst drive that can arise when the body becomes depleted of water, when the effective osmotic pressure of body fluids increases as a result of excess solute intake, or when the concentration of certain humoral factors in the circulation increases.[2-4] Conversely, after adequate or excess ingestion of water, inhibitory influences on thirst and fluid intake arise that are also of a regulatory nature. In this article we consider the brain regions and neural mechanisms that participate in the stimulation and inhibition of thirst.

Traditionally, textbooks of physiology refer to the hypothalamus as the site of a thirst center. The concept of a center is somewhat outmoded these days, and consideration of neural circuitry regulating fluid intake is probably a more realistic approach. The hypothalamus achieved such status as a thirst center mainly as a result of the pioneering work of the Swedish physiologist Andersson and McCann,[5] who were able to obtain stimulus-bound drinking of water in animals (goats) with electrical stimulation of electrodes that had been implanted surgically into the hypothalamus. Earlier, Anders-

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son[6] had shown that chemically stimulating the hypothalamus with injections of hypertonic saline also could stimulate drinking. Although some interpreted these results as evidence that the thirst osmoreceptor was located in the hypothalamus, Andersson[6] himself was particularly careful in the interpretation of these data because he was aware that the concentration of NaCl in the solutions injected was supraphysiologic and the spread of the stimulus was not controlled. In addition, early studies of hypothalamic lesions, particularly in the lateral hypothalamic area, that resulted in adipsia and aphagia, also influenced the idea of a thirst center in the hypothalamus.[7,8] Besides the hypothalamus, several other brain regions that include the medulla oblongata, midbrain, and cerebral cortex participate in the homeostatic regulation of water intake and thirst. These brain regions are considered in the context of sensors or receptor sites for circulating hormones, integrative regions that relay thirst signals within the brain, or as cortical effector sites.

Effector Sites in the Cerebral Cortex

Thirst has been described as one of the primal or homeostatic emotions. Similar to the experience of hunger, full bladder, lack of breath, or fatigue, thirst is a subjective state of the conscious brain that demands a response—in the case of thirst, the ingestion of water is the response. Because thirst is a function of the conscious brain, it has been assumed that regions of the cerebral cortex have a role in the generation of this homeostatic emotion. Supporting this assumption is evidence that decorticate rats, in which the forebrain has been separated from the brainstem, are unable to regulate water intake in response to osmotic stimuli.[9]

The most extensive electrophysiologic survey of the cortical regions that may participate in the generation of thirst was made by Robinson and Mishkin.[10] They stimulated numerous cortical sites in conscious monkeys and observed stimulus-bound water drinking at several loci. The anterior cingulate cortex was the site at which electrical stimulation most reliably resulted in water drinking, although drinking responses also were obtained less frequently by stimulation of the putamen and substantia nigra, the substantia innominata and diagonal band, the preoptic region, lateral hypothalamus, and ventral tegmentum.

In recent years, we have performed neuroimaging studies of thirsty human beings using positron emission tomography or functional magnetic resonance imaging (fMRI). Hypertonic saline was infused intravenously to stimulate thirst in the patients being imaged and regional cerebral blood flow was correlated with their thirst scores.[11,12] These studies have revealed several cortical regions that became activated in human patients with the onset of thirst (Fig 1), this activation being extinguished with satiation of thirst by the drinking of water. The cortical sites that consistently showed a correlation between activity and thirst score (ie, they became activated as patients became thirsty and inactive as thirst decreased) in both positron emission tomography and fMRI studies were the anterior and posterior cingulate cortex, parahippocampal gyrus, insular cortex, precentral gyrus, and parts of the cerebellum.[11,12]

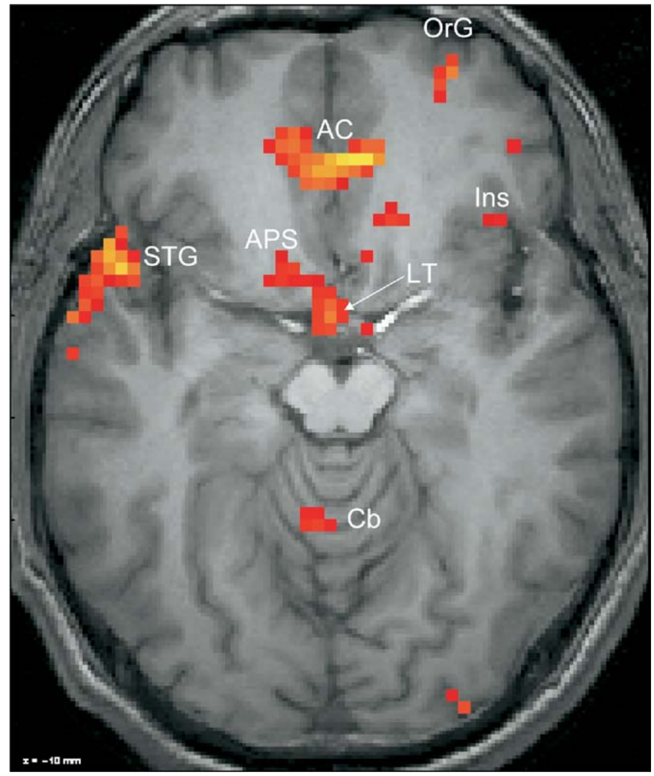

Figure 1 fMRI highlighting areas of significant increase in blood oxygen dependent (BOLD) signal in a human patient experiencing strong thirst in response to an intravenous infusion of hypertonic saline. A horizontal plane ($z = -10$) 10 mm below the level of the anterior commissure is shown. Pseudocolor images are shown with yellow and red areas indicating regions of increased activity. Areas implicated in the generation of thirst are the anterior cingulate cortex (AC), cerebellum (CB); insula (INS), and lamina terminalis (LT). Other regions of activation indicated are the anterior perforated substance (APS), orbital gyrus (ORG), and the superior temporal gyrus (STG). Reproduced with permission from Egan et al.[12]

Such correlations unfortunately do not allow us to define the role of the particular cortical regions mentioned earlier in the generation of thirst, however, some general comments can be made regarding the anterior cingulate, insular, and parahipppocampal regions of the cortex. Several homeostatic emotions such as deep pain, air hunger, or thirst cause both the anterior cingulate and insular cortices to be activated. Craig[13,14] proposed that homeostatic emotions such as thirst, hunger, or deep pain reflect an adverse condition within the body that requires a behavioral response and suggested that a specific sensation may be engendered in the interoceptive anterior insular cortex, whereas an affective motivation may be generated in the anterior cingulate region. For the evocation of thirst in this scenario, specificity for the interoceptive modality of thirst might be a function of a particular part of the insula. It is not surprising that activation of the parahippocampal gyri, which are implicated in memory, may be associated with thirst stimuli, because memory of water