the next section. The term thirst means different things in different circumstances. Its original definition referred to a sensation that people say they have when they are dehydrated. Here I use it in a descriptive sense. Because we do not know how other animals feel, thirst simply means a tendency to seek water and to ingest it.

**OSMOMETRIC THIRST**

Osmometric thirst occurs when the solute concentration of the interstitial fluid increases. This increase draws water out of the cells, and they shrink in volume. The term osmometric refers to the fact that the detectors are actually responding to (metering) changes in the concentration of the interstitial fluid that surrounds them. Osmosis is the movement of water through a semipermeable membrane from a region of low solute concentration to one of high solute concentration.

The existence of neurons that respond to changes in the solute concentration of the interstitial fluid was first hypothesized by Verney (1947). Verney suggested that these detectors, which he called osmoreceptors, were neurons whose firing rate was affected by their level of hydration. That is, if the interstitial fluid surrounding them became more concentrated, they would lose water through osmosis. The shrinkage would cause them to alter their firing rate, which would send signals to other parts of the brain. (See Figure 11.5.)

When we eat a salty meal, we incur a pure osmometric thirst. The salt is absorbed from the digestive system into the blood plasma; hence, the blood plasma becomes hypertonic. This condition draws water from the interstitial fluid, which makes this compartment become hypertonic as well and thus causes water to leave the cells. As the blood plasma increases in volume, the kidneys begin excreting large amounts of both sodium and water. Eventually, the excess sodium is excreted, along with the water that was taken from the interstitial and intracellular fluid. The net result is a loss of water from the cells. At no time does the volume of the blood plasma fall.

Most researchers now believe that osmoreceptors responsible for osmometric thirst are located in the region of the anterior hypothalamus that borders the anteroventral tip of the third ventricle (the AV3V). Buggy et al. (1979) found that injections of hypertonic saline directly into this region produced drinking.

Research supports the basic nature of Verney’s hypothetical osmoreceptors (Bourque, 2008). Zhang et al. (2007) found that osmoreceptors are a special kind of mechanoreceptor that transduces changes in the volume of the cell into changes in membrane potential, and hence in neural firing rate. They also found that actin filaments are necessary for the osmoreceptors’ sensitivity to changes in cell volume. (You will recall that the mechanoreceptors responsible for detection of sound vibrations in the inner ear also contain actin filaments.) The investigators placed a micropipette against the membranes of individual osmoreceptors and found that the application of pressure or suction could alter the membrane potential of the cells. For example, if a cell was exposed to a hypertonic solution, the cell lost water and its membrane potential fell. If pressure was then applied, the volume of the cell increased and the membrane potential returned to normal. (See Figure 11.6.)

A functional imaging study by Egan et al. (2003) found that the human AV3V also appears to contain osmoreceptors. The investigators administered intravenous injections of hypertonic saline to normal subjects while their brains were being scanned. They observed strong activation of several brain regions, including the AV3V and the anterior cingulate cortex. When the subjects were permitted to drink water, they did so and almost immediately reported that their thirst had been satisfied. Simultaneously, the activity in the anterior cingulate cortex returned to baseline values. However, the activity in the AV3V remained high. These results suggest that the activity of the anterior cingulate cortex reflected the subjects’ thirst, which was immediately relieved by a drink of water. (As we saw in Chapter 7, activity of this region is related to people’s perception of the unpleasantness of painful stimuli.) In contrast, the continued activity in the AV3V reflected the fact that the blood plasma was still hypertonic. After all, it takes around 20 minutes for a drink of water to be absorbed into the general circulation. As we saw in the discussion of Figure 11.2, satiety is an anticipatory mechanism, triggered by the act of drinking.

**osmometric thirst** Thirst produced by an increase in the osmotic pressure of the interstitial fluid relative to the intracellular fluid, thus producing cellular dehydration.

**osmoreceptor** A neuron that detects changes in the solute concentration of the interstitial fluid that surrounds it.
The fall in the activity of the anterior cingulate cortex appears to reflect the activation of this putative mechanism. (See Figure 11.7.)

Two other functional imaging studies (Farrell et al., 2006; Xiao et al., 2006) confirm that thirst activates the anterior cingulate cortex. An anatomical tracing study by Hollis et al. (2008) showed that in rats, osmoreceptive neurons in the AV3V were connected to the cingulate cortex via the dorsal midline nuclei of the thalamus. This pathway between the osmoreceptors in the AV3V and the cingulate cortex is probably responsible for the activation seen in the functional imaging studies.

**VOLUMETRIC THIRST**

Volumetric thirst occurs when the volume of the blood plasma—the intravascular volume—decreases. As we saw earlier, when we lose water through evaporation, we lose it from all three fluid compartments: intracellular, interstitial, and intravascular. Thus, evaporation produces both volumetric thirst and osmotic thirst. In addition, loss of blood, omitting, and diarrhea all cause loss of blood volume (hypovolemia) without depleting the intracellular fluid.

Loss of blood causes pure volumetric thirst. From the earliest recorded history, reports of battles note that the wounded survivors called out for water. In addition, because hypovolemia involves a loss of sodium as well as water (that is, the sodium that was contained in the ionic fluid that was lost), volumetric thirst leads to a salt appetite.

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**FIGURE 11.6 Action of an Osmoreceptor.** Actin filaments in brain osmoreceptors detect changes in solute concentration in the interstitial fluid when the cell membrane expands or contracts. Changes in cell volume cause changes in the membrane potential, which serve as the signal for osmotic thirst. (a) When hypotonic solution was added to the culture medium of an isolated osmoreceptor, the cell volume increased and the membrane potential decreased. When suction was then applied through the micropipette, the cell volume decreased and the membrane potential increased. (b) Opposite effects were seen when cell volume was reduced by a hypertonic solution and then increased by applying pressure through the micropipette.


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**FIGURE 11.7 Osmotic Thirst in Humans.** Functional MRI scans show brain activation produced by osmotic thirst. (a) Activation in the anterior cingulate cortex and hypothalamus, corresponding to a sensation of thirst. (b) Activation in the lamina terminalis, the location of the brain’s osmoreceptors.

The Role of Angiotensin  

The kidneys contain cells that are able to detect decreases in the flow of blood to the kidneys. The usual cause of a reduced flow of blood is a loss of blood volume; thus, these cells detect the presence of hypovolemia. When the flow of blood to the kidneys decreases, these cells secrete an enzyme called renin. Renin enters the blood, where it catalyzes the conversion of a protein called angiotensinogen into a hormone called angiotensin. In fact, there are two forms of angiotensin. Angiotensinogen becomes angiotensin I, which is quickly converted by an enzyme to angiotensin II. The active form is angiotensin II, which I shall abbreviate as AII.

Angiotensin II has several physiological effects: It stimulates the secretion of hormones by the posterior pituitary gland and the adrenal cortex that cause the kidneys to conserve water and sodium, and it increases blood pressure by causing muscles in the small arteries to contract. In addition, AII has two behavioral effects: It initiates both drinking and a salt appetite. Therefore, a reduction in the flow of blood to the kidneys causes water and sodium to be retained by the body, helps to compensate for their loss by reducing the size of the blood vessels, and encourages the animal to find and ingest both water and salt. (See Figure 11.8.)

Little Billy started eating salt. He had always liked plenty of salt on his food, but his craving finally got out of hand. His mother noticed that a carton of salt lasted only a few days, and one afternoon she caught Billy in the kitchen with the container of salt on the counter next to him, eating something out of his hand. It was salt, pure salt! She grabbed his hand and shook the salt out of it into the sink and then put the container on a shelf where Billy couldn’t reach it. Billy started crying and said, "Mommy, don’t take it away—I need that!"

The next morning she heard a crash in the kitchen and found Billy on the floor, an overturned chair next to him. Clearly, he was trying to get at the salt. "What’s wrong with you?" she cried. Billy sobbed and said, "Please, Mommy, I need some salt! I need it!" Bewildered but moved by his distress, she reached down the container and poured some salt in his hand, which he ate eagerly.

After consulting with the family physician, Billy’s parents decided to have him admitted to the hospital, where his bizarre craving could be investigated. Although Billy cried piteously that he needed salt, the hospital staff made sure that he received no more than a child normally needs. He tried several times to leave his room, presumably to try to find some salt, but he was brought back, and the door to his room was finally locked. Unfortunately, before definitive testing could be begun, Billy died.

The diagnosis of Billy’s craving came too late to help him. A disease process had caused his adrenal glands to stop secreting aldosterone, a steroid hormone that stimulates the kidneys to retain sodium. Without this hormone, excessive amounts of sodium are excreted by the kidneys, which causes the volume of the blood to fall. In Billy’s case the fall in blood volume that occurred when his access to salt was blocked led to a fatal loss of blood pressure. This unhappy story occurred several decades ago, and we can hope that physicians today would recognize an intense salt craving as a cardinal symptom of adrenal insufficiency.

Angiotensin acts on neurons found in one of the organs of the brain located outside the blood–brain barrier, the subfornical organ (SFO) (Phillips and Felix, 1976; Simpson, Epstein, and Camardo, 1978). This structure gets its name from its location, just below the commissure of the ventral fornix. Neurons in the SFO send their axons to the median preoptic nucleus (not to be confused with the medial preoptic nucleus), a small nucleus wrapped around the front of the anterior commissure, a fiber bundle that connects the amygdala and anterior temporal lobe. Neurons in the median preoptic nucleus then communicate with the motor systems involved in drinking. (See Figure 11.9.)