More Than the Brain's Drain

Does cerebrospinal fluid help the brain convey messages?

By JOHN TRAVIS

It may lack the majesty of the mighty Mississippi, but there's a vital river running through your head.

This neurological stream consists of cerebrospinal fluid (CSF), a clear, colorless liquid that constantly bathes the brain and spinal cord. The average person has about 150 milliliters, less than a cupful, of this fluid within his or her body. Suggesting a new importance for CSF, some scientists are now arguing that its currents carry important signals for sleep, appetite, and sex.

Tissue called the choroid plexus, deep inside the brain, secretes most of the CSF. The fluid, which is about 99 percent water, starts its journey from the two lateral ventricles, which are side-by-side cavities in the upper brain, and then travels down to the third ventricle and on to the fourth, which is near the brain stem. From there, it either wells up over the brain's surface or flows down the spinal canal. Ultimately, it's absorbed into the bloodstream.

Since scientists discovered CSF, several roles have been recognized for the liquid. It helps provide the nervous system with a steady supply of nutrients. The brain also literally floats in CSF, which dramatically reduces the weight pressing down upon the spine.

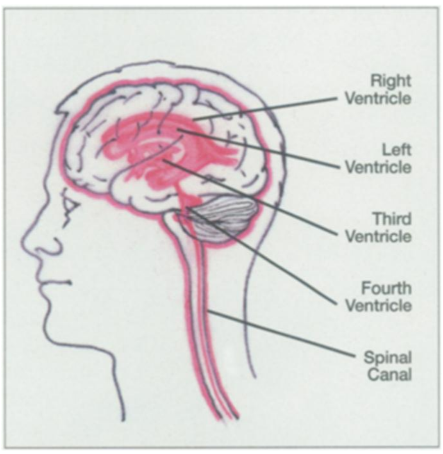
Furthermore, the fluid provides a watery padding that protects the brain's fragile cellular network. Blows to the head would cause significantly more damage if CSF weren't there to absorb and diffuse the impact.

Finally, since it's replaced several times a day, CSF flushes the central nervous system. Biologists have compared cerebrospinal fluid to urine, another liquid created in the body that removes harmful substances.

"The [traditional] view is that the cerebrospinal fluid is the drainage system of the brain," notes Michael N. Lehman of the University of Cincinnati College of Medicine.

While not dismissing these long-recognized roles, Lehman and a small group of scientists recently gathered to discuss whether this thin broth plays an even more active role. At a Society for Neuroscience symposium in Los Angeles last November, they offered provocative evidence that CSF may actually comprise a river of information within the central nervous system.

The neuroscientists are quick to admit that they haven't yet proven that the body uses cerebrospinal fluid to send messages. "We're posing the question and determining the strength of the evidence," says Rae Silver of Columbia University.



Cerebrospinal fluid (red) forms in brain cavities called ventricles and flows over the surface of the brain or through the spinal canal.

Lehman and Silver organized the recent symposium because of an interest that grew out of their studies of the suprachiasmatic nuclei (SCN). This small region of the mammalian brain controls the daily, or circadian, rhythms of animals, including people. The SCN was thought to exert its influence by sending electrical signals to other areas of the brain via nerve cell connections.

Yet Lehman, Silver, and their colleagues found evidence that a soluble chemical released by the SCN acts as a circadian signal. They had encased SCN tissue in a polymer capsule, which they implanted into the ventricles of hamsters whose own SCN tissue had been destroyed. The capsule prevented the nerve cells within from making connections to those outside. The encapsulated transplants nonetheless restored many of the animals' lost circadian rhythms, the researchers reported several years ago.

The SCN had previously been found to rhythmically secrete substances—the hormone vasopressin, for example—into CSF. Since the capsule allows chemicals to diffuse through it, Lehman and Silver speculated that in their experiments, a diffusible circadian signal was transmitted within the liquid to targets throughout the brain. Such a signal molecule has not yet been identified.

Other researchers have documented that molecules drifting in CSF can penetrate the brain. Miles Herkenham of the functional neuroanatomy section at the National Institute of Mental Health in Bethesda, Md., described at the symposium an example of such work.

His research team injected a radioactively labeled form of inulin, a carbohydrate molecule that stays outside cells, into rodents' brain CSF and then monitored the marker's location. Herkenham showed in dramatic time-lapse images that within 4 hours, inulin had suffused the extracellular space of the whole brain.

Other researchers have shown that even larger molecules, such as proteins that stimulate the growth of nerve cells, can depart from CSF and diffuse through brain tissue. "There is a potential, if you wait long enough, for these molecules to go long distances," says neuroscientist Charles Nicholson of the New York University Medical Center.

Given that potential, the question remains whether some areas of the brain release substances into the cerebrospinal fluid that signal other regions or perhaps the whole brain.

Some of the earliest research to hint at communication skills of CSF was performed on sleep-deprived animals, James M. Krueger of Washington State University in Pullman told the symposium. Scientists observed many years ago that when they injected CSF from such animals into the ventricles of normally rested animals, sleep resulted. "There's something in cerebrospinal fluid that's transferable and induces sleep," says Krueger.

In fact, there are many such sleep-inducing substances in CSF (SN: 6/10/95, p. 356). Krueger's research group concentrates on interleukin-1, a protein originally implicated in the functioning of the immune system. The investigators have found that interleukin-1 most effectively induces sleep when it is injected into the subarachnoid space, the CSF-filled region covering the surface of the brain.

The researchers are now trying to determine whether CSF normally carries interleukin-1 to the sleep-triggering region of the brain. While the protein's concentration in CSF definitely increases as animals become sleep-deprived, the CSF might merely receive overflow from the brain rather than being the medium through which a command to sleep travels, says Krueger.

Appetite might be under the sway of CSF. Scientists have identified several substances that stimulate eating when injected into the brain. The most potent is a small protein called neuropeptide Y (SN: 7/27/96, p. 63).

Satya P. Kalra of the University of Florida in Gainesville and his colleagues have been working to determine how the brain uses this neuropeptide to regulate eating. When they implanted a pump that constantly releases the peptide into the CSF-filled ventricles of rodents, the animals "eat and eat and eat," says Kalra.

Neuropeptide Y is normally present in CSF, which makes Kalra and his colleagues suspect that the fluid carries the peptide to the hypothalamus, the brain region where the molecule seems to act to produce feeding behavior. Moreover in fasting animals, cells near the ventricles release the peptide, he notes.

Reproduction is as basic a function as sleeping and eating, and scientists suspect cerebrospinal fluid may influence it as well. Donal C. Skinner of the National Institute of Agronomy Research in Nouzilly, France, reported at the Los Angeles symposium that gonadotropin-releasing hormone (GnRH) appears in the CSF of sheep. The hormone's concentrations there rise and fall roughly in parallel with its abundance in blood.

Secreted primarily by the hypothalamus, GnRH normally stimulates the brain's pituitary gland to make luteinizing hormone and follicle-stimulating hormone. These two hormones drive the creation of eggs or sperm and, ultimately, sex hormones such as estrogen and testosterone. Curiously, Skinner says that the GnRH in cerebrospinal fluid does not seem to reach the pituitary gland.

Studies have suggested that GnRH also influences sexual behavior in many animals. One form of the hormone, for example, elicits courtship behavior in sparrows when it's injected into the birds' ventricles. Skinner's team is now studying whether the hormone's presence in the CSF bathing the brain regulates sheep sexual behavior.

The hormone melatonin is another candidate for a message conveyed by cerebrospinal fluid, Skinner's colleague Benoit Malpaux told the symposium participants. Produced by the brain's pineal gland, this hormone regulates many daily biorhythms; it induces sleep, for example. It can also govern seasonal reproductive activity.

Since the pineal gland and the brain cells that melatonin targets are located close to the third ventricle, Malpaux suggests that the gland secretes the hormone directly into CSF. Indeed, he reports, the concentrations of melatonin in sheep's CSF are much higher than in their blood. The hormone follows a similar daily cycle in both fluids: Concentrations rise at night and fall during the day.

Determining the capabilities of cerebrospinal fluid is not just an academic exercise. In the Jan. 24, 1998 LANCET, for example, Edward Rubenstein of Stanford University noted that, with age, the brain's choroid plexus calcifies, which leads to a dramatic decline in the production of CSF. He suggests that changes in CSF physiology contribute to dementia in some elderly people.

Fully testing such a hypothesis, however, won't be possible until neuroscientists better understand the roles played by the brain's small, but mighty, river. □