Heart Peptide Goes to the Head

As part of the brain's security system, the blood-brain barrier is very selective about what passes through its gates. Yet there's a glitch in this arrangement of rigid checks and balances: It is particularly susceptible to fluid buildup in head injuries and certain diseases. The central nervous system's handling of this dangerous edema has been little understood. But recent research indicates that it may be a case of the heart controlling at least a part of the brain.

James A. Nathanson and Luca Steardo of Harvard Medical School and Massachusetts General Hospital in Boston report in the Jan. 23 SCIENCE that brain barrier tissues carry receptors for a cardiac peptide – and that this peptide can affect the rate of spinal fluid production. Some researchers believe the peptide could have treatment implications for edema within the next decade.

Secreted by the heart, the hormone – called atrial natriuretic peptide (ANP) or atrial natriuretic factor – can act as a diuretic, influencing fluid movement. It was discovered in the heart less than a decade ago; subsequent studies of its role in sodium and water regulation nominated the peptide as a possible treatment for hypertension (SN: 1/17/87, p.42). Although its receptors have been found elsewhere in the body, most notably in the kidney, the Boston study is the first to describe ANP action at the crucial blood-brain interface.

The brain's barrier system essentially has two parts: the blood-brain barrier, made up of endothelial cells lining the brain's blood vessels (see adjacent story), and the blood-cerebrospinal fluid (CSF) barrier, made up of the epithelial cells of the choroid plexuses. Found deep inside the brain, the choroid plexuses are network structures that produce CSF, which in turn "cushions" the central nervous system. Nathanson and Steardo focused their search for ANP receptors on the choroid epithelium from rabbits.

Biochemical assays showed that the isolated cells were "very heavily enriched" with receptors for the peptide, according to Nathanson. He told SCIENCE NEWS that the ANP mechanism at the brain barriers is significant for reasons that go beyond its possible role in regulating fluid volume. "It may be the first clear example of a membrane-associated receptor that activates guanylate cyclase directly," he says.

That particular enzyme is responsible for production of guanosine 3′,5′-monophosphate (cGMP), found throughout the body and possibly important in mediating hormonal action.

Because the cells so rich in ANP receptors also produce CSF, the researchers used catheterized rabbits to examine the effects of the peptide on CSF production. Injection of ANP caused an average 35 percent drop in CSF secretion in the rabbits. Parallel studies of ANP injected into the eye showed a drop in intraocular pressure.

Why does the body have a fluid-regulating cardiac peptide with far-flung receptor sites, one that decreases CSF output and increases cGMP production? The final answers await further research, but the significance of ANP research is not disputed, says a review article in the Jan. 16 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA). Clinical trials in the United States and elsewhere show infusion of the peptide makes blood pressure quickly drop, which has attracted the interest of pharmaceutical companies since one in five adults suffers from high blood pressure.

But ANP treatment of fluid-retention conditions like that found in congestive heart failure may precede treatment for hypertension, according to the JAMA article. Aram V. Chobanian, director of the Cardiovascular Institute at Boston University School of Medicine, was quoted in JAMA as saying that ANP might be used to treat edema within five to 10 years. But he cautions that it may be much longer before this naturally occurring hormone is used as a blood pressure drug.

It is too early, Nathanson says, to know whether ANP will be useful in treating cerebral edema, a serious threat in strokes, cerebral hemorrhage, infections, tumors and head trauma. Nonetheless, the choroid epithelial cell system should provide an accessible model for further ANP study. *– D.D. Edwards*

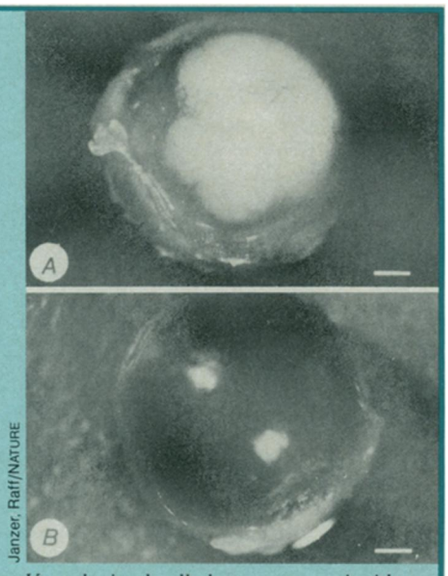
Brainy ties that bind

An understanding of the workings of the blood-brain barrier – so miserly about what passes from the blood to the brain – has been sought by scientists for more than a century. Nearly 20 years ago, tight junctions were described between the endothelial cells of cerebral capillaries. Subsequent experiments showed that the ability of those cells to build the barrier is not intrinsic in endothelial cells, but is instead induced by their presence in the nervous system. Now, there is new evidence identifying which brain cells provide the signal to "get tight."

One specialized brain cell, the astrocyte, has long "feet" that wrap around capillaries and is thought to be active in the cross-membrane transport of certain substances, including potassium. But astrocytes apparently stimulate junction formation in endothelial cells as well. British scientists Robert C. Janzer and Martin C. Raff of University College London report in the Jan. 15 NATURE that the astrocytes are responsible for "inducing blood-brain barrier properties" in the endothelial cells.

Using cells grown on the surface of the iris in rats, as well as on the membranes of chick embryos, Janzer and Raff found that the "tissue lumps" formed by astrocytes – which after several days were ingrown with blood vessels made up of endothelial cells – did not absorb blue dye injected into the animals' circulatory systems.

As pointed out in an accompanying article by N. Joan Abbott of King's College London, evidence from this and other studies suggests that the inducing signal is a diffusible substance, secreted by some population of astrocytes. Abbott notes that the Janzer-Raff discovery does not answer all the questions: For instance, in some non-mammalian brains and in certain areas of the mammalian brain, the barrier is not always at the endothelial layer. *– D.D. Edwards*



Janzer, Raff/NATURE

Vascularized cell clumps grown inside the eyes of rats for two weeks illustrate the tight junctions induced by astrocytes. After the rats are intravenously injected with a dye, the astrocyte cell clump (A) remains unstained, while a meningeal cell clump (B) is darkly stained. (The two white spots are artifacts.) Scale bars = 1mm.