42 Production and Flow of Cerebrospinal Fluid

Conrad E. Johanson

Continuously flowing cerebrospinal fluid (CSF) enables a clean extracellular fluid for efficient neurotransmission. The choroid plexus, the main source of CSF, homeostatically secretes ions/molecules into the ventricle to maintain pH, potassium (K+) concentration, and osmolality. Streaming of CSF supports several distributive functions. CSF volume transmission (bulk flow) down the neuraxis conveys vitamins, neurotrophins, and proteins for metabolic/structural support of the brain. Neurohormones and immunomolecules in plasma normally move across the blood-CSF interface, distributing to central regions for neuroendocrine and immunoregulation. The choroid plexus has sensory as well as secretory roles. Chemical receptors in choroid epithelium respond to CSF neurochemical changes, as in stroke, by secreting trophins to heal injured brain regions. When intracranial pressure increases, CSF formation is compensatorily decreased by central fluid–regulatory hormone inhibition at choroid epithelial receptors. At night, augmented CSF flow penetrates cortical paravascular spaces (the glymphatic system) to flush interstitial waste products outward to cervical lymph. Sleep deprivation hampers glymphatic excretion. Aging choroid plexus displays histologic/oxidant damage and curtailed CSF-forming capacity. Patients with idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer disease have CSF production decline, ventricular dilation, and glymphatic impairment; consequently, brain fluids stagnate and metabolism wavers as CSF turnover rate dwindles. MRI-derived geriatric data for aqueductal/cervical flows, pathway resistance, and compliance inform decisions on surgical/medical interventions. Therapeutic innovations to attain sound CSF dynamics and relieve neural disorders should include stabilizing the aging choroid plexus, ependyma, and brain capillaries.

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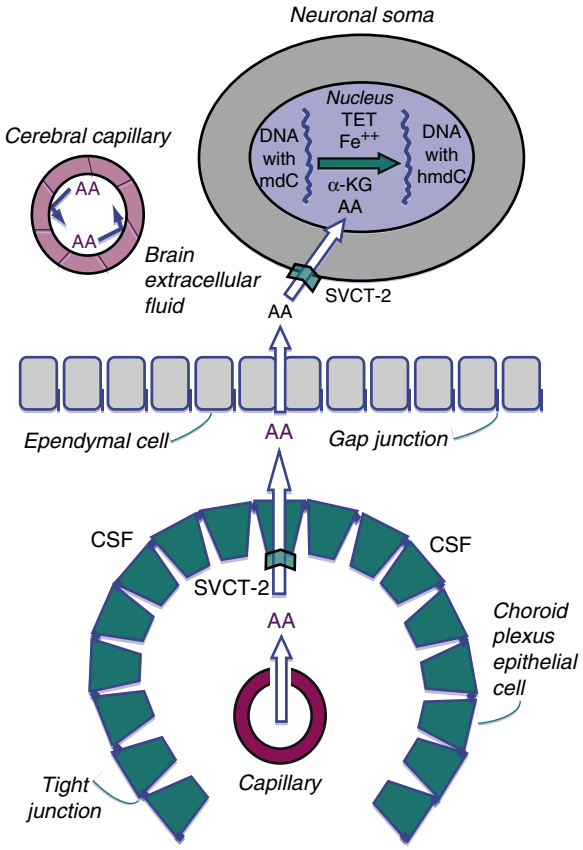

Choroid plexus–cerebrospinal fluid (CSF) nexus as the sole distributor of vitamin C into the brain. For substances not transported across the blood-brain barrier, regulated transport by the choroid plexus alternately supplies neurons. Distribution of ascorbic acid (AA) by the choroid plexus–CSF into the brain is essential for metabolic needs, including cofactoring for neuronal DNA reactions: AA in plasma is reflected by the inside surface of impervious endothelium and tight junction (upper left), thus AA does not penetrate the blood-brain barrier; rather, AA reaches neurons indirectly via the choroid plexus, CSF, and ependyma. Accordingly, AA moves (unfilled arrow) from leaky vessels in the choroid plexus to epithelial cells (bottom panel) for transport into the CSF by the Na+-dependent vitamin C transporter 2 (SVCT-2). From the CSF, AA diffuses through permeable ependyma into the interstitial fluid and also likely enters cortical perivascular spaces by bulk flow (see Fig. 42.7). Within neuronal nucleoplasm (upper right), AA is a cofactor for the 10-11 translocation enzymes (TET), with Fe++ and α-ketoglutarate (KG), to oxidize methyldeoxycytidine (mdC) molecules in DNA to hydroxymethyldeoxycytidine (hmdC). SVCT-2 transporters concentrate AA in CSF and neurons, maintaining neuronal concentrations at millimolar levels. (*From Spector R, Johanson CE. The nexus of vitamin homeostasis and DNA synthesis and modification in mammalian brain. Mol Brain. 2014;7:3.*)

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KEY CONCEPTS

- The choroid plexus secretes most of the ventricular cerebrospinal fluid (CSF) and regulates its pH/ions as well as its volume and pressure.
- Cephalocaudad CSF volume transmission (bulk flow) from lateral ventricles to basal cisterns delivers vitamins, neurotrophic factors, and peptides to multiple brain regions.
- The choroid plexus–CSF mediates central neuroendocrine and immune actions by regulating transport of hormones and immune molecules/leukocytes across the blood-CSF interface.
- Chemical sensors in the choroid plexus epithelium respond to changes in neurochemical and immune molecules in CSF by secreting trophic molecules to heal injured brain regions.
- To control intracranial pressure, fluid formation by the choroid plexus decreases compensatorily in response to increasing titers of CSF neurotransmitters and fluid-regulating neuropeptides.
- Nocturnally increased CSF flow promotes glymphatic flushing of brain interstitial waste to lymph drainage sites; chronic glymphatic blockage predisposes to neurodegeneration.
- Noninvasive MRI assessments of aqueductal flow and brain compliance to predict shunting outcome also help evaluate CSF hydrodynamic changes in neural diseases.
- In aging, idiopathic normal pressure hydrocephalus (iNPH), and Alzheimer disease, dwindling CSF formation and ventriculomegaly cause harmful stagnation of CSF turnover rate.
- To maintain healthy fluid dynamics in older adult patients, novel biomedical strategies are needed to maintain viable choroid plexus–CSF flow routes and brain capillary function.

CSF secreted by the choroid plexus dynamically affects the neuronal milieu. Diverse choroidal regulations mediate homeostasis of fluid composition, volume, and pressure. One of several transport interfaces in CNS, the choroid plexus–CSF performs work to complement the blood-brain barrier (BBB), ependyma, and pia mater (Fig. 42.1). Known as the *blood-CSF barrier* (BCSFB), the choroidal epithelium carries out abundant transport/secretory actions that aid the brain. Epithelial cell ultrastructure (Fig. 42.2) reveals a high capacity of organelles to form fluid and adapt to changes in CSF neurochemistry.

Over a lifespan, adverse physico-chemical stressors and diseases (e.g., hydrocephalus, stroke, and Alzheimer disease [AD]) strike the CSF-brain nexus.[1] Sensors/receptors in the choroid plexus[2] detect elevated intracranial pressure (ICP)[7] and biochemical/biophysical harm to the peripheral nerve,[3] spinal cord,[4] and injured brain.[5,6] Adjustive responses by choroid plexus elements then help repair injury and restore milieu balance at distant regions of the nervous system. Breakdown of the homeostatic reserve of the choroid plexus in senescence and neurodegeneration jeopardizes the ability of the CSF to maintain brain well-being. This chapter discusses the neurosurgical aspects of adult choroid plexus–CSF secretions and flow, relative to brain fluid balance in health and disease.

DIFFERENT FLUID-FORMING CAPABILITIES: CHOROID PLEXUS VS. BRAIN CAPILLARIES

The master generator of ventricular CSF is the choroid plexus (see Figs. 42.2 to 42.4). Continuously produced CSF implements stability of CNS extracellular fluid ions and volume. During the day and at night, the choroid epithelia churn out fluid. Ventricular CSF formation is ~0.4 mL/min/g choroid plexus for several mammals and is somewhat less for humans. Nascent CSF is more than a passive ultrafiltrate of plasma.[8] Active secretion by choroidal epithelium is exquisitely modulated so that ICP is stable when CSF absorption is normal. One-tenth of the choroidal blood flow of ~4 mL/min/g[9,10] becomes new CSF in the ventricles. Volume relationships among plexus blood flow, choroid cell size, and fluid output are regulated by hormones.[11]

Multisource evidence indicates that 60% to 70% of CSF is formed by plexuses in the lateral third and fourth ventricles.[8] It is rarely challenged that the choroid plexus is the cardinal source of ventricular CSF.[12] Current[8,13] and historical[14,15] overwhelming evidence points to the choroidal tissue as the main origin of CSF.[16,17] Clinical cauterizations of choroid plexus[18] lower ICP, further evidence that ventricular CSF originates largely from choroidal tissues.[19] A lavish *net* turnover of fluid at the blood-CSF interface is energized by high blood flow to the plexus,[10] substantial activities of Na^+-K^+-ATPase[20,21] and carbonic anhydrase,[22–24] and numerous ion transporters.[25] In sum, the choroid plexus is operationally geared for great fluid turnover.

On the other hand, *net* formation of *fluid* at the BBB (see Fig. 42.1) is much slower[26] than at the choroidal BCSFB. Actually, substantial bidirectional H_2O *exchange* at the BBB may be faster than choroidal CSF production[27]; however, this cerebral capillary H_2O exchange flux is not a true *net fluid secretion* by capillaries. Such primary fluid-secretory capacity difference between CNS transport barriers manifests in that BBB Na^+ transport (linked to H_2O transfer) is insensitive to acetazolamide (Diamox) inhibition of carbonic anhydrase,[28] in contrast with inhibitable Na^+ transport by the ICP-sustaining choroid plexus fluid generator. Thus evidence is lacking that cerebral capillaries form a CSF-like HCO_3^--rich fluid, the active secretion of which helps set intraventricular pressure. Additionally, the choroid plexuses greatly affect ventricular CSF volume and composition.

CEREBROSPINAL FLUID ION HOMEOSTASIS

A hallmark function of CSF is BCSFB regulation of CSF ions. Perturbed levels of ions in plasma are minimally transferred to CSF as a result of (1) choroid plexus permeability barriers (tight junctions) and (2) active ion transporters (efflux reabsorption of ions that leak into CSF). Neurochemical stability, essential to synaptic functional integrity, is affected by ion fluxes at the blood-CSF interface (choroid and arachnoid membranes). Stable cation and anion composition characterizes CSF,[29] even in neurodegeneration.[30] Brain extracellular ion concentration stability, particularly CSF K^+, promotes efficient neurotransmission.

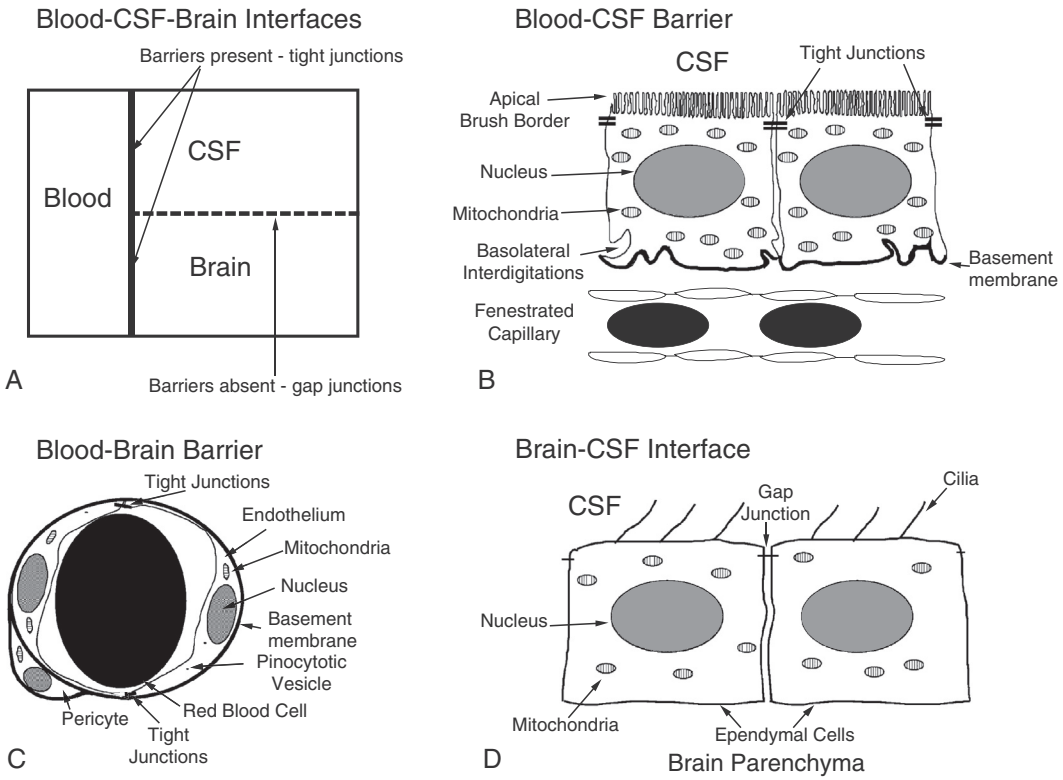

Figure 42.1. Structural configuration of transport interfaces in the adult central nervous system. (A) Restrictive tight junctions at the choroidal blood–cerebrospinal fluid (CSF) barrier (BCSFB) demarcate blood from ventricular CSF. A 10-fold tighter barrier (than the choroid plexus) separates brain capillary blood from tissue *(bold solid line).* The permeable ependyma, with gap junctions, divides ventricular CSF from the brain's internal face *(broken line);* similarly, the leaky pia-glia membrane overlies the external cortical surface. (B) The choroidal BCSFB has a single epithelial layer spot-welded by zonulae occludentes tight junctions at the apices of the cells. Choroidal capillaries permit large molecules to penetrate the interstitium up to the basolateral membrane. Lush microvilli at the CSF-facing apical membrane provide a great area for transport. There is also marked surface area in the interdigitating basolateral membranes. Copious mitochondria energize the dynamic transport of ions and substrates. (C) The anatomic substrate for the blood-brain barrier is the tight junctions between endothelial cells. A profusion of mitochondria powers bidirectional solute transport across abluminal and luminal endothelial faces. Transendothelial movement of molecules into the brain also occurs by pinocytosis. The microvessel wall is expansively covered by astrocyte foot processes and pericytes, furnishing added regulation of transport and permeability. (D) The CSF-brain interface contains ependyma, with gap junctions highly permeable to macromolecules distributing readily between ventricles and brain interstitial fluid. Transependymal bidirectional distribution of solutes allows the CSF to act as a nutritional source as well as an excretory sink for cerebral catabolites. (*From Smith DE, Johanson CE, Keep RF. Peptide and peptide analog transport systems at the blood-CSF barrier. Adv Drug Deliv Rev. 2004;56[12]:1765–1791.*)

Several multivalent ion transporters in choroid epithelium actively maintain steady CSF levels. Extracellular Ca^{++} and Mg^{++} affect neuronal excitability; these divalent cations are actively translocated by the plexus to attain CSF concentrations, respectively, below and above those in plasma. A dozen different choroidal Zn^{++} transporters[31] provide substantial CSF zinc for glutamatergic neurons. Because of impeded diffusion at CNS barriers, an actively regulated supply of multivalent ions in CSF fluid formation mediates a gamut of neuronal modulations.

INTRICATE FLUID BALANCE AMONG CENTRAL NERVOUS SYSTEM COMPARTMENTS

To preserve sound ICP and volume, the CNS relies on a battery of choroidal and extrachoroidal fluid-regulating mechanisms.[8] Orderly CSF percolation depends on precisely controlled solute and H_2O fluxes at several transport interfaces separating blood, CSF, and brain.[32–34] Extrachoroidally, the ependyma (see Fig. 42.1), glia, leptomeninges,[35] and parenchyma have complementary roles, perhaps responsible for one-third of healthy intracranial fluid formation. For the past half century, the pharmacologic manipulation and isolated preparations of choroid plexus have consistently demonstrated fluid formation. Similar direct evidence for extra-choroidal fluid production is less extensive. The many systematic studies of choroid plexus allow CSF investigators to regard this tissue as primary in ventriculocisternal flow dynamics.

The choroidal secretory epithelium also affects parenchyma/interstitium by supplying pulsatile CSF movement for "priming" the cerebral glymphatic flow. Disturbed CSF flow in aging and from mass blockages compromises extensive exchange between large-cavity CSF and brain interstitial fluid (ISF).[36] Accordingly, a diminished CSF formation rate in senescence and disease[37] disrupts pressure gradients and drainage flow routes in the CNS.

VARIATIONS IN CEREBROSPINAL FLUID PRODUCTION: NORMAL VS. DISEASE

CSF dynamics affect central metabolism; thus it is necessary to assess optimal CSF formation rate in health. Adult humans

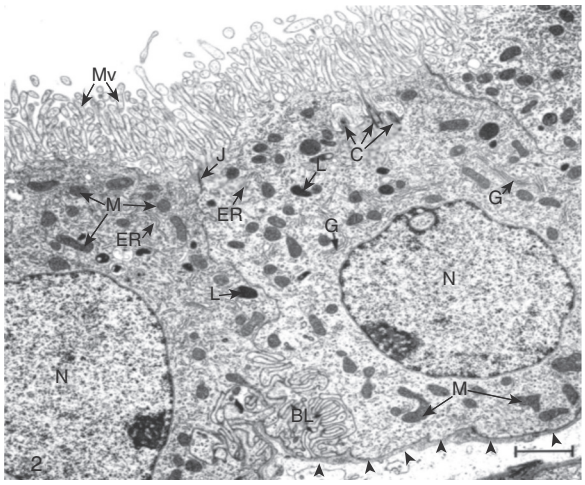

Figure 42.2. Ultrastructure of adult choroid plexus epithelial cell. A prominent feature is the profusion of apical membrane microvilli *(Mv)* at the cerebrospinal fluid–facing surface. Numerous mitochondria *(M)* sustain the energy needs of a great variety of transport processes at both poles of the epithelium. *J* signifies the junctions welded tightly together, where two epithelial cells attach at their apices. The oval nucleus *(N)* contains a nucleolus. *ER* and *G* refer to the endoplasmic reticulum and Golgi apparati, respectively. *C* refers to a centriole. The basal labyrinth *(BL)* is the intertwining of basolateral membranes of adjacent cells. *Arrowheads* point to basal lamina at the plasma face; this lamina separates the choroid cell above from subjacent interstitial fluid (scale bar is 2 μm). Choroidal tissue sampled from the lateral ventricle of a rat; fixative was OsO_4. *L,* Lysosome. (*Modified from Johanson CE, Duncan JA 3rd, Klinge PM, Brinker T, Stopa EG, Silverberg GD. Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. Cerebrospinal Fluid Res. 2008;5[1]:10.*)

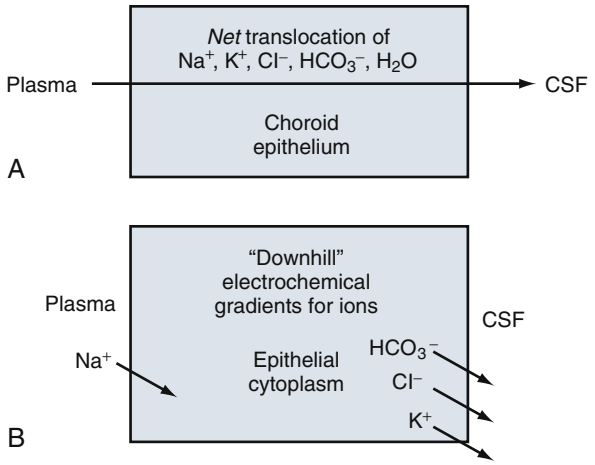

Figure 42.3. Ionic gradients across choroid plexus membranes that drive secretion of cerebrospinal fluid (CSF). (A) Continual streaming across the choroid plexus of CSF, a fluid rich in Na^+, K^+, Cl^-, and HCO_3^-, occurs from regulated transport/permeability to various ions and H_2O. (B) Following active extrusion of Na^+ by the choroid plexus into the CSF, a downhill gradient for Na^+ is set up across the opposite basolateral membrane. This inward Na^+ gradient promotes transfer of plasma-derived Na^+ into the choroidal epithelium via ion cotransport or exchange. The Cl^-, HCO_3^-, and K^+ that are loaded into choroid plexus are subsequently released via channels or cotransporters down electrochemical gradients into ventricular CSF. (*From Johanson CE, Duncan JA 3rd, Klinge PM, Brinker T, Stopa EG, Silverberg GD. Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. Cerebrospinal Fluid Res. 2008;5[1]:10.*)

normally form choroidally derived CSF at ~0.35 mL/min.[8,38] Nocturnally elevated CSF production[39] likely modifies cerebral metabolism and CSF clearance of catabolites during sleep. Sleep disorders diminish excretion of brain waste products at night.

CSF formation fluctuates in neurologic disease.[40] Neurosurgeons face situations in which the choroid plexus forms excess or inadequate fluid volume. Inflammation of choroid plexus–CSF[41] by excess tumor necrosis factor[42] or from CSF hemorrhage increases the CSF formation rate. Thus in certain patients, altered barrier transport and CSF dynamics may be controlled by reducing choroid plexus–CSF inflammation.[43,44] With *hypersecreting* choroidal papillomas,[45,46] surgical excision often reduces ICP. With a *hyposecreting* choroid plexus in normal pressure hydrocephalus (NPH) and AD, the stagnated CSF turnover rate[47,48] injures the brain by retaining toxic proteins/catabolites in ISF. Severely impaired choroid plexus–CSF dynamics harm cranial neurons[36] (e.g., in hydrocephalus and neurodegeneration), thereby requiring surgical/medical remediation.

MECHANISMS OF CEREBROSPINAL FLUID FORMATION BY THE CHOROID PLEXUS

Ions penetrate the CNS in large part across the choroid plexus.[8,16] Control of brain fluid balance therefore starts with knowledge of choroidal transport mechanisms. Fluid secretion into the ventricles is mediated by an array of ion transporters asymmetrically positioned at the blood- and CSF-facing membranes. Structurally and functionally, the choroidal epithelium resembles the proximal tubule.[49] Renal-like organs are designed to transfer copious volumes of fluid.[16]

CSF production is directly proportional to *net* transfer of Na^+ and Cl^- from the blood to the ventricles.[50–52] Reduced Na^+ and Cl^- transport across the choroid plexus into the CNS attenuates CSF formation.[20,53] The driving force for ion movements across choroidal membranes is an energetically *downhill* concentration or electrochemical gradient. At the external-limiting membranes, the gradient direction for Na^+, Cl^-, K^+, and HCO_3^- is given in Fig. 42.3. Na^+ entry into the choroid epithelium is *downhill* (gradientwise) from the plasma across the basolateral membrane.

On the other side of the cell, K^+, Cl^-, and HCO_3^- move *downhill* across the apical membrane into the CSF. Basolaterally and apically, these *downhill* ionic movements are set up by *uphill* active transport (requiring chemical energy as ATP) via the primary Na^+ pump (Fig. 42.4). Active Na^+ pumping into the CSF keeps choroid cell Na^+ concentration relatively low,[20] thereby establishing a basolateral inward-driving force on Na^+ transport from the plasma into the epithelium.[54]

Epithelial transport polarity enables fluid formation. Polar distribution (sidedness) of specific active transporters and passive channels enables *net* fluid movement (blood to CSF; see Fig. 42.4). Basolateral (interstitial) and apical (CSF) transporters and channels thus mediate streaming of ions and H_2O. Directionally in CSF formation, the fluxes are mainly from the choroid plexus interstitium to the epithelial parenchyma to the ventricles. Fig. 42.4 schematizes the primary and secondary active ion transporters. Apical channels allow passive diffusion of K^+ and Cl^- into nascent CSF.[55] Several cationic species participate in CSF production, such as K^+, Mg^{++}, and Ca^{++}. However, fluid

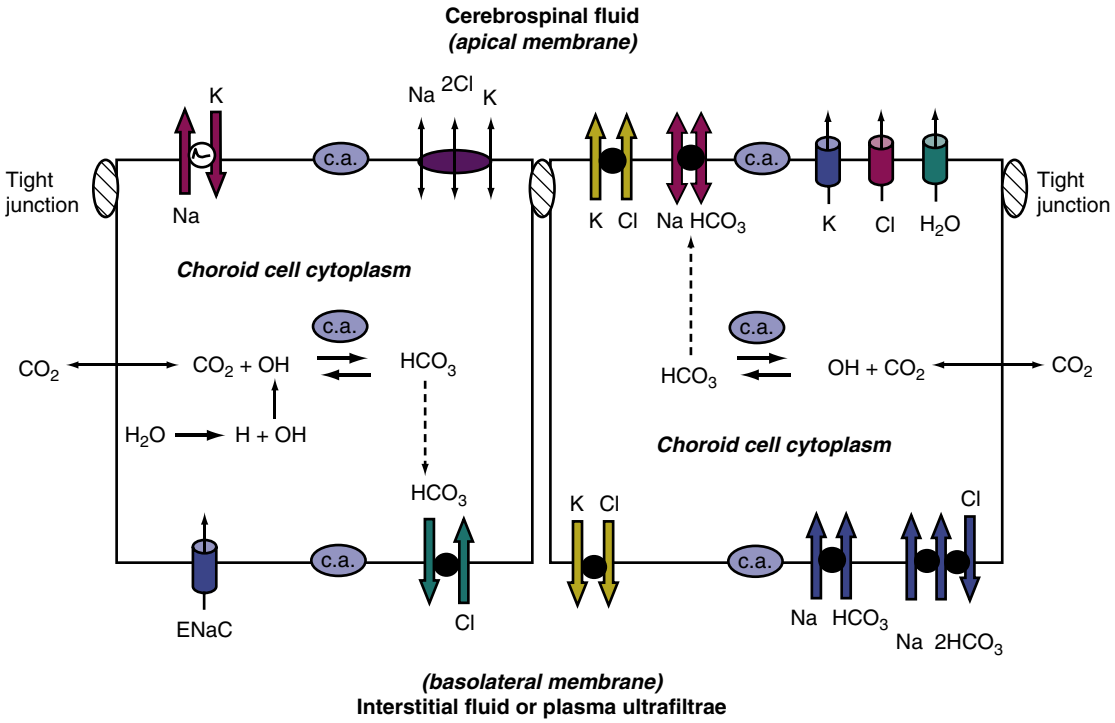

Figure 42.4. Choroid plexus basolateral and apical membrane transport mechanisms involved in cerebrospinal fluid (CSF) formation and homeostasis.[38] Interstitial Cl^- is actively accumulated by choroidal epithelium via Cl^- transporters in the basolateral membrane. The epithelial Na^+ channels (ENaCs) are on the plasma face of choroid cells[60]; ENaC conductance facilitates diffusion of Na^+ down a steep electrochemical gradient, from the interstitial fluid into the epithelium. Interstitial HCO_3^- is actively taken up by carrier linkage with Na^+ transport into the cell. Additional HCO_3^- is generated intracellularly by carbonic anhydrase *(c.a.)* activity. Following cytoplasmic swirling to the apical side, intracellular K^+, Cl^-, and H_2O diffuse via channels down gradients from the cytoplasm into the CSF. Na^+ and HCO_3^- move into the ventricles by apical membrane cotransporters. Na^+ is also actively extruded into the CSF by the Na^+ pump, which cycles K^+ across the apical membrane. KCl cotransport helps stabilize epithelial cell volume as CSF is formed. CSF production is essentially the net transport of Na^+, K^+, Cl^-, HCO_3^-, and H_2O from the blood to the ventricles. (*From Johanson CE, Duncan JA 3rd, Klinge PM, Brinker T, Stopa EG, Silverberg GD. Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. Cerebrospinal Fluid Res. 2008;5[1]:10.*)

formation is primarily generated by *net* secretion of Na^+, Cl^-, and HCO_3^-. Water osmotically follows ion transport across the apical membrane (see Fig. 42.4). Such transfers occur by stepwise (sequential) and parallel processes, which are described in the following sections.

Sodium

Energetically, the pivotal initiating step in CSF formation is primary active transport of Na^+ from the choroidal epithelium to the ventricle.[56] Na^+-K^+-ATPase activity empowers Na^+ pumping (see Fig. 42.4) by generating ATP. To stabilize choroid pH and epithelial volume[54,57] in CSF elaboration, the apical Na^+ efflux is balanced by continuous basolateral Na^+ influx with HCO_3^- (via carrier slc4a10) and possibly by the epithelial Na^+ channel (ENaC; diffusion).[58–60] Transport primacy of slc4a10 (Na^+-dependent Cl^--HCO_3^- exchange) is manifested by reduced ion transport into the choroid plexus–CSF (with decreased ventricular volume) when slc4a10 activity is disrupted.

Chloride

As the main anion in CSF, Cl^- is actively transported across the basolateral membrane in exchange for cellular HCO_3^-.[61] This pulls plasma Cl^- into the epithelium, accumulating above electrochemical equilibrium.[62] Under some conditions, intraepithelial Cl^- diffuses into the CSF via the efflux arm of the Na^+-K^+-Cl^- cotransporter.[63] However the *downhill* diffusion of Cl^- into the CSF via apical Cl^- channels is likely also a prominent pathway by which Cl^- accesses the ventricles to sustain fluid formation.[55]

Bicarbonate

HCO_3^- in the choroid plexus has a dual source. First, carbonic anhydrase catalyzes hydration of CO_2 to H^+ and HCO_3^- in the choroid epithelium.[22] In addition, HCO_3^- is pulled from the plasma into the epithelium by Na^+-coupled HCO_3^- transport.[58] On accumulation, the HCO_3^- is available for release across the CSF-facing membrane via two mechanisms. In the first route, HCO_3^- in the epithelium diffuses *downhill* via an anion channel into the CSF.[64] In the second route, HCO_3^- is transferred via an electrogenic Na^+-coupled HCO_3^- cotransporter at the apical membrane.[57,65] The critical maintenance function of this Na^+-HCO_3^- cotransport carrier to CSF is revealed by gene knockout, yielding a phenotype of collapsed ventricular volume and ICP as well as disrupted CSF ion homeostasis.[66] HCO_3^--rich nascent CSF reflects facilitated movement of this labile anion into the ventricles as CSF is produced.[67] Acidic products of brain metabolism and subarachnoid hemorrhage[68] are countered in part by choroid plexus HCO_3^- secretion.

Water

CSF is 99% H_2O. The watery medium of CSF enables multiple buffering, distributive, and excretory functions,[8] thus it is significant to characterize H_2O movement across the choroid plexus. Following Na^+, Cl^-, and HCO_3^- transport into the CSF, H_2O chases these osmotically active ions into the ventricles by diffusing down its chemical potential gradient through aquaporin 1 (AQP1) channels in the apical membrane.[33,69] AQP1 channel involvement in CSF formation is deduced from AQP1 knockout mice displaying substantially reduced fluid movement into the ventricles.[70] As a result, ICP is lowered.[71] The Na^+-K^+-$2Cl^-$ cotransporter (apical membrane) also facilitates the cell-to-CSF movement of H_2O. Such transcellular H_2O movement is potentially a drug target to modify CSF dynamics.[33]

Steroid hormones as well as agents structurally related to acetazolamide, furosemide, and bumetanide modulate H_2O traffic through AQP1 channels and via Na^+-K^+-$2Cl^-$ cotransport.[33,72] Rates of H_2O delivery, arterial blood–to–ventricular CSF, are now assessable by tracer-free MRI; this enables quantification of how H_2O movement across the BCSFB affects ventricular volume.[73]

VOLUME TRANSMISSION OR BULK FLOW OF CEREBROSPINAL FLUID

The quantitatively great transfer of H_2O molecules across the choroid plexus into the ventricles sets up vital actions mediated by bulk-flowing CSF. Thus CSF, as a convecting fluid, transfers to the brain many types of ions/molecules[17] secreted at the BCSFB: trace elements, inorganic ions, proteins, growth factors, neurotrophic agents, immunomolecules, hormones, and nucleosides.[74] In Fig. 42.5, vitamin C is used to exemplify the principles of choroid plexus–CSF transport/distribution to neurons by volume transmission (see Fig. 42.5). Accordingly, CSF has an indispensable nutritive/trophic distributive function that is dependent on healthy fluid dynamics.

Critical excretory roles are also performed by CSF bulk flow. Sink action, to dispose of unwanted molecules in CNS, depends on continuously streaming CSF from the choroid plexus (Fig. 42.6). Organic anion metabolites and brain "spilling" of excess K^+ and amino acids/neurotransmitters into CSF are normally removed by ventricular bulk-flow clearance. Harmful retention of potentially toxic cellular products, as in certain neural diseases, occurs consequent to diminished sink action following dysregulated CSF flow or formation.

NEUROHUMORAL REGULATION OF CEREBROSPINAL FLUID FORMATION RATE

CSF formation rate adjustment is part of managing disordered ICP or ventricle size.[8,75] Manipulating choroidal ion transporters and channels is key for finer control of epithelial fluid output. From a cell physiology standpoint, there are multiple regulatory loci. Targeting strategies used to modulate choroidal secretion are: (1) manipulating levels of neurotransmitter/neuropeptide ligands for receptors on epithelial membranes interfacing extracellular fluid and (2) using diuretic agents to inhibit membrane-bound proteins that effect ion/H_2O fluxes. Experiments focus on *reducing* CSF formation because both nature and clinicians try to minimize increases in ICP.

Neurohumoral Ligands/Receptors

Apical and basolateral membranes of the choroid plexus contain receptors for biogenic amines and fluid-regulating peptides. Neurogenic tone on CSF formation is commonly inhibitory.[76] Adrenergic regulation of the choroid plexus epithelium is substantial, including modulation of Na^+-K^+-ATPase and carbonic anhydrase activities. The superior cervical ganglion innervates the lateral ventricle choroid plexus. Sympathetic nerve stimulation and resection, respectively, decreases and increases CSF production by ~30%.[77] Pharmacologic/biochemical evidence indicates that sympathomimetic lowering of CSF formation results from a combination of β-receptor inhibition of epithelial secretion and α-receptor stimulation (vasoconstriction-reduced plexus blood flow).[76] Cholinergic agents also decrease CSF production, indicating muscarinic receptor inhibition of the

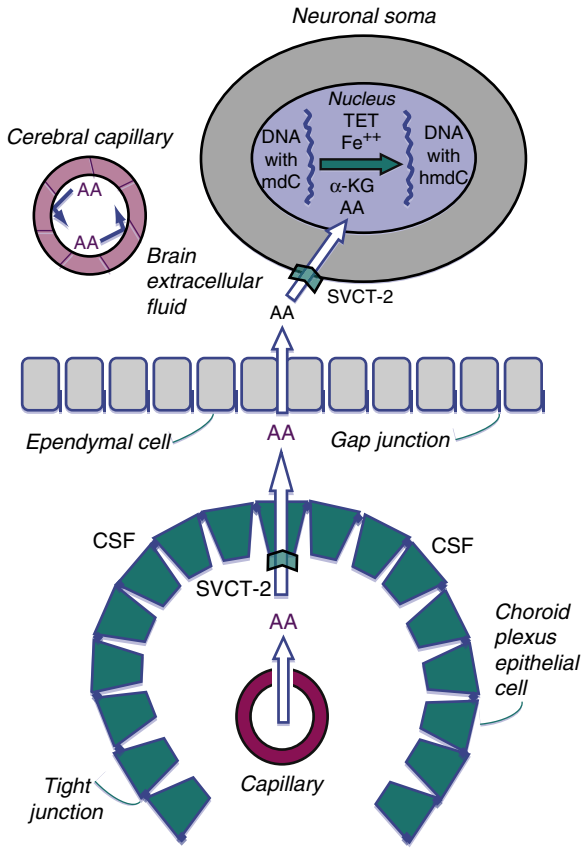

Figure 42.5. Choroid plexus–cerebrospinal fluid (CSF) nexus as the sole distributor of vitamin C into the brain. For substances not transported across the blood-brain barrier, regulated transport by the choroid plexus alternately supplies neurons. Distribution of ascorbic acid *(AA)* by the choroid plexus–CSF into the brain is essential for metabolic needs, including cofactoring for neuronal DNA reactions: AA in plasma is reflected by the inside surface of impervious endothelium and tight junction *(upper left),* thus AA does not penetrate the blood-brain barrier; rather, AA reaches neurons indirectly via the choroid plexus, CSF, and ependyma. Accordingly, AA moves *(unfilled arrow)* from leaky vessels in the choroid plexus to epithelial cells *(bottom panel)* for transport into the CSF by the Na^+-dependent vitamin C transporter 2 (SVCT-2). From the CSF, AA diffuses through permeable ependyma into the interstitial fluid and also likely enters cortical perivascular spaces by bulk flow (see Fig. 42.7). Within neuronal nucleoplasm *(upper right),* AA is a cofactor for the 10-11 translocation enzymes *(TET),* with Fe^{++} and α-ketoglutarate *(KG),* to oxidize methyldeoxycytidine *(mdC)* molecules in DNA to hydroxymethyldeoxycytidine *(hmdC).* SVCT-2 transporters concentrate AA in CSF and neurons, maintaining neuronal concentrations at millimolar levels. (*From Spector R, Johanson CE. The nexus of vitamin homeostasis and DNA synthesis and modification in mammalian brain. Mol Brain. 2014;7:3.*)

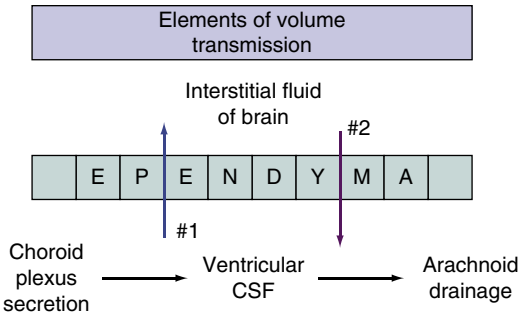

Figure 42.6. Volume transmission of cerebrospinal fluid (CSF) for intra–central nervous system (CNS) distributive actions. CSF flow originates as choroid plexus secretion that convects solutes throughout the ventriculosubarachnoid space nexus. The hydrostatic pressure head generated by choroid plexus secretion "pushes" CSF throughout the CNS. This streaming process is slowed down by Diamox (acetazolamide) inhibition of fluid formation. In transit to arachnoidal drainage sites, the CSF exchanges solutes between the ventricles/subarachnoid space and the brain interstitial fluid (ISF). Transthyretin, cystatin C, growth factors, and vitamins from the choroid plexus penetrate the ISF *(arrow #1)* across the permeable ependyma. Endocrine signaling by hormone transit from the choroid plexus to the CSF to the hypothalamus is mediated by CSF bulk flow to the third ventricle. Simultaneously, surplus amino acids and excess "spillover" K along with unneeded proteins and catabolic organic anions move *(arrow #2)* from the ISF into the CSF for clearance. As both a nutrient supplier and waste repository, CSF volume transmission mediates solute/cell distribution along diverse extracellular pathways (see Fig. 42.7). (*Modified from Johanson CE, Duncan JA 3rd, Klinge PM, Brinker T, Stopa EG, Silverberg GD. Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. Cerebrospinal Fluid Res. 2008;5[1]:10.*)

choroid plexus. Accordingly, sympathetic and parasympathetic tone both suppress CSF formation.

Serotonin 5-HT_{2C} receptors in the choroid plexus, expressing at high levels, find wide use in pharmacologic studies[78] of CSF formation. Serotonin and serotoninergic agonists perfused through the ventricles reduce CSF production.[79] Localization of 5-HT_{2C} receptors to the choroid plexus apical membrane points to CSF formation control via centrally released 5-HT. CSF serotonin in 5-HT fibers course the ependymal wall[80] and discharge into the ventricles (see Fig. 42.1) for convection to the choroid plexus. Binding of 5-HT to apical receptors inhibits CSF formation.

The fluid-modulating peptides arginine vasopressin (AVP), angiotensin II, and atrial natriuretic peptide (ANP) reduce CSF formation when exogenously placed in the ventricles. This fits with central neuroendocrine control of CSF mediated by receptors at the apical membrane.[38] Moreover, CSF concentration of AVP and ANP is regulated centrally, that is, independently of plasma. This points to neuroendocrine regulation of CSF dynamics[81] via receptor stimulation at the *central* (apical) side of the choroid plexus.

Peptides figure prominently in transport, permeability, and modulation at the blood-CSF interface.[82,83] Neuropeptide regulation of choroidal fluid output helps adjust ICP elevation. Both AVP and ANP induce dark, neuroendocrine-type choroid epithelial cells that inhibit CSF production, especially in hydrocephalus.[84,85] AVP modulation of CSF formation includes functional interactions in the choroid plexus with basic fibroblast growth factor[86,87] and angiotensin II.[88] AVP directly inhibits epithelial ion transport[89] and constricts choroid plexus vessels, thereby reducing choroidal blood flow and curtailing CSF formation.

ANP is of interest in peptidergically controlling CSF dynamics. Autoradiographic mapping of choroidal binding sites reveals ANP receptor plasticity[85] in response to hydrocephalus and CSF fluid shifting (space flight). In humans, ANP in CSF is independent of plasma levels[90] but increases in proportion to ICP increments.[91] Interestingly, intracereboventricular ANP *decreases* the CSF formation rate in animal models[92] in spite of *increasing* plexus blood flow. Systemically, ANP unloads expanded plasma volume by inducing natriuresis. ANP may also unload CSF excess. Central ANP deserves attention as a regulator of CSF pressure by feedback servomechanistic effects on epithelial ion transport (through cGMP modulation) and lower CSF production.

PHARMACOLOGIC INHIBITION OF CEREBROSPINAL FLUID FORMATION

Diuretics reduce CSF production. The strategy is to suppress fluid formation without altering CSF composition. A desirable outcome is to lower ICP by decreasing fluid input to the ventricles. Of clinical significance is whether the inhibitor is administered on the blood side or the CSF side. Tight junctions between choroid epithelial cells limit penetration of H_2O-soluble agents via diffusion across the BCSFB. Hydrophilic agents such as ouabain and furosemide (potent inhibitors of apical Na^+-K^+-ATPase and Na^+-K^+-$2Cl^-$ cotransport) barely reduce Na^+ transport and CSF formation when presented to blood[20]; on presentation to CSF, these drugs halve fluid production. Thus drug access to transporter target is a salient pharmacokinetic factor.

Dual apical transporter targets are the Na^+ pump and Na^+-K^+-$2Cl^-$ cotransporter. Cardiac glycosides directly inhibit Na^+ pumping. Intraventricular ouabain reduces CSF formation[93] but unfortunately elevates CSF K^+.[20] Digoxin, which is more lipid-soluble, permeates the BCSFB to reach target sites on the ventricular side. Digoxin-treated patients have lower CSF formation by ~25%.[94] Older adult patients on digoxin may have a risk for neurotoxicity as a result of reduced CSF turnover plus low baseline CSF production in senescence.[48]

Another CSF-facing membrane target is bumetanide-sensitive Na^+-K^+-$2Cl^-$ cotransport.[95] Bumetanide acts on the kidney to excrete retained peripheral fluid. It has also been tested on the choroid plexus, which is sometimes referred to as the "kidney" of the CNS.[49] When presented intraventricularly (0.1 mM) in dogs, bumetanide curtails CSF production ~50%.[96] Intravenous bumetanide negligibly affects CSF formation[97] as a result of poor access to the choroidal apical membrane. Furosemide, another high-ceiling diuretic, also reduces CSF formation and ICP when given via CSF.[98] At high doses, furosemide alters choroidal blood flow, carbonic anhydrase activity, and ion cotransport. A third pharmacologic target on the CSF-facing membrane is the Na^+-HCO_3^- cotransport,[65] which is awaiting analysis of effects on CSF dynamics.

Basolateral membrane targets for fluid production are Cl^--HCO_3^- exchange, the HCO_3^--loading transporters, and possibly the Na^+ channel. The diuretic amiloride inhibits ENaC and Na^+-H^+ exchange; relatively high doses lower CSF formation.[28] Acetazolamide, a suppressor of CSF formation,[99] increases choroid cell pH, leading to reduced Na^+ uptake by the choroid plexus[22]; this carbonic anhydrase inhibitor may also impede H_2O movement through AQP1.[72]

With regard to basolateral Cl^--HCO_3^- exchange, disulfonic stilbene agents interfere with Cl^- uptake and reduce CSF formation[100]; but consequent peripheral H^+/CO_2 distortions complicate clinical usage. The HCO_3^--loading transporters on the plasma side of the choroid plexus[101,102] need evaluation in CSF dynamics. Pharmacologic control of basolateral Na^+-dependent Cl^--HCO_3^- exchange (slc4a10) may help manage disease-induced changes in CSF volume and flow.[8]

LOWER CEREBROSPINAL FLUID FORMATION RATE IN HYDROCEPHALUS

Structurally and functionally, the choroid plexus is markedly altered in hydrocephalus.[84] There are smaller choroidal solute fluxes[103–105] and CSF formation rate[37,106] in congenital and adult chronic hydrocephalus. This is a response to augmented CSF volume and pressure. Reduced choroidal blood flow, shrunken (damaged) epithelial cells, and diminished surface area for blood-CSF transport contribute to less fluid turnover in hydrocephalus.[84,103,104]

Two non–mutually exclusive mechanisms, physical and physiologic, explain how elevated CSF pressure reduces fluid formation: (1) *Physically*, the elevated ventricular pressure (ICP) in hydrocephalus opposes and thereby decreases net fluid filtration across plexus capillaries,[107] the initial step in CSF formation. This physical factor, by Starling's law, reduces availability of H_2O, ion, and substrate to the plasma-facing membrane of the choroid plexus. Consequently, as the choroidal perfusion pressure gradient (mean arterial pressure [MAP] minus ICP) is lowered, the plasma ultrafiltrate feeding CSF formation is compromised by the smaller hydrostatic pressure gradient (inward to tissue) across the capillaries. (2) *Physiologically*, a putative servomechanism operates such that as ICP is increased, there is a consequent release of neurohumoral agents to initiate a choroid epithelial receptor–mediated decline in CSF production. The many neurotransmitters/hormones that inhibit CSF formation give weight to this neuroendocrine model.[85,108]

In humans with NPH, the CSF formation rate decreases ~40% as estimated by the Masserman technique.[37] Masserman-derived findings for aging CSF production have not been consistently corroborated by MRI.[109] However, in adult rats injected with kaolin (i.e., an NPH-like model), the CSF formation rate plummets by ~40%.[104,110] In kaolin hydrocephalus, the shifting of rodent choroid plexus AQP1 protein[111] from the apical membrane (functional) to cytoplasmic vesicles (non-functional) fits the suppressed CSF dynamics. Overall, the moderately elevated CSF pressure, by several mm Hg, in human NPH and kaolin models devastates the CNS interior. CSF hypertension damages choroid plexuses, ependyma (see Fig. 42.1), and periventricular zones. Therapeutic agent stabilization of the gradually increasing CSF pressure in adult chronic hydrocephalus or late-stage AD[112] may therefore lessen brain damage.

FLOW DIRECTIONALITY OF CEREBROSPINAL FLUID

Direction, routes. and velocity of CSF flow vary greatly in health, posture, and life stage. Flow directionality is significant because altered CSF dispersal routes can adversely affect neural systems. Normal CSF flow oscillation during inspiration (anterograde flow) and expiration (retrograde flow) minimize unhealthy stagnation of fluid/metabolites. Markedly variable aqueductal flow direction occurs in certain diseases, such as intracranial aneurysms.[113] Sex and age influence forward as well as backward aqueductal volume flows.[114]

As a result of ependymal ciliary activity (see Fig. 42.1), vectors for local currents are set up in the ventricle to establish flow directionality of CSF containing neurons (stem cells) for targeted distribution.[115] This directed flow expedites delivery of factors to progenitor cells in neurogenic zones around lateral ventricles. Organized bundles of motile ciliary networks in the third ventricle guide CSF streaming of signaling molecules that modulate the hypothalamus.[116] Critical hydrodynamic functions of cilia manifest when mutated ciliary genes disrupt ventricular CSF flow.

CSF flow steadily moves to exit sites in the arachnoid and possibly the cerebral capillaries, under certain conditions. In supine healthy adults, CSF flows from the lateral ventricles to the third ventricle, through the Sylvian aqueduct to the fourth ventricle, and then to the basal cisterns and SAS. From the SAS, the CSF distributes to venous and lymphatic drainage areas (e.g., parasagittal dura).[117] CSF outflow reaches multiple drainage sites, where arachnoid membranes interface the SAS CSF with venous blood and lymph (e.g., the superior cervical glands).

IMPACT OF CEREBROSPINAL FLUID FLOW ON BRAIN FUNCTIONS

Inefficient CSF flow is harmful physically and neurochemically. Free flow of CSF is biophysically necessary for efficient CNS absorption of arterial pressure pulses.[118] Biomechanically, gravitational effects (1 g force on earth vs. microgravity in space flight) importantly influence CSF flow distribution.[119] Biochemically, uninterrupted CSF flow sustains delivery of substrates to stabilize neuronal functions,[38] including modulation of DNA metabolism by folate/ascorbate derived from choroid plexus transport.[120] Growth factors and peptides in free-flowing CSF support neuronal/glial metabolism and injury responses. Stagnated CSF impairs cognition by slowing solute exchange. Clearance functions are impaired by CSF stasis because toxic metabolites do not efficiently flush away from neuronal networks.

CSF motion depends on *upstream* choroidal, *mainstream* ventriculocisternal, and *downstream* arachnoidal fluid throughput. Obstructions cause regional flow impairment. Impeded CSF movement and circulatory interactions with ISF[121] impair synapses and neurotransmission.[36] Until recently, CSF *flow* characteristics were less studied than pressure/volume phenomena. Brain injury exacerbated from attenuated CSF flow has prompted research on regional ventricular CSF interactions with adjacent ISF and blood flow.[122]

CSF flow is not laminar or constantly unidirectional. Pulsating CSF massages leptomeningeal arteries to drive glymphatic outflow from the CNS.[123] In the cardiac pumping cycle, there is anterograde caudal flow (systole) followed by retrograde cranial flow (diastole). This cyclic forward-and-backward fluid motion in the aqueduct is a passive response to arterial pulsations and brain compliance. Thus the cyclic flow is driven by a dynamically changing hydrostatic pressure gradient that is superimposed on the static pressure gradient driving bulk flow of CSF from proximal choroid plexus origins to distal arachnoid drainage sites.

MAGNETIC RESONANCE IMAGING OF CEREBROSPINAL FLUID HYDRODYNAMICS VS. HEMODYNAMICS

Elucidating CSF dynamics requires delineation of patient physiology and "standardization" of MRI parameters/sequences. Otherwise, patient-to-patient comparison of CSF measurements has limited value. Cine phase-contrast MRI quantifies CSF flow noninvasively and rapidly. CSF flow velocity is conveniently assessed in the aqueduct. Typically with MRI, the velocity sensitization (or encoding) for the aqueduct is twice that of the cervical SAS. CSF flow velocity increases in the narrow aqueduct of Sylvius. In addition to the "pipe" size, the driving force from the pressure gradient across the aqueduct affects CSF flow.

Various methods are used to measure hyperdynamic pulsatile flow in the aqueduct. Average flow rate (mL/min) and stroke volume (net caudal flow, μL, over cardiac cycle) are useful. Mean flow rates >18 mL/min is a criterion for NPH. Early studies of stroke volume, assessing flow, reported favorable shunt surgery (i.e., improved Hakim triad) for patients with stroke volume >42 μL; however, other studies differ.[124,125] While hyperdynamic flow >18 mL/min may diagnose NPH, mild or normal pulsatile flow in the aqueduct cannot be excluded.[124,125]

Other CSF regions assessed are the third ventricle floor (third ventriculostomy context[126]), the cervical (C2) SAS,[127] and the prepontine cistern.[128] Questions linger, but hyperdynamic CSF

TABLE 42.1 Dynamic Fluid Flows During the Systolic Phase of the Cardiac Cycle

Phase Number	Percent of Cardiac Cycle	Description of Flow Phenomena in Various CNS Compartments
1	0	Systolic arterial Fi peak occurs in the internal carotid arteries, causing an instantaneous increase in cerebral blood volume.
2	5	Cervical CSF initially responds to brain expansion by flushing through the SAS.
3	11–20	In response to cervical CSF displacement, SAS pressure decreases, leading to peak flow (flush) through the jugular veins.
4	20–25	In response to SAS pressure decrease, the third ventricle–aqueductal CSF surges distally (downward).
5	25–35	Cerebral pressures equilibrate as arterial and venous flows equalize; cervical CSF flow becomes negligible.

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *Fi,* flow (in); *SAS,* subarachnoid space.

Data recapitulated from Stoquart-ElSankari S, Baledent O, Gondry-Jouet C, Makki M, Godefroy O, Meyer ME. Aging effects on cerebral blood and cerebrospinal fluid flows. J Cereb Blood Flow Metab. 2007;27(9):1563–1572.

assessment may prove valuable for managing CSF diversion in hydrocephalus. Phase-contrast balanced steady-state free precession, higher signal-to-noise ratio, and insensitivity to turbulent flow improves CSF flow quantitation.[128]

CSF flow is intricately coupled with cerebral blood flow. Analyses of hydrodyamic-hemodynamic relationships provide disease differentials. Throughout the cardiac cycle, a typical MRI-generated CSF flow curve has opposite phases covering flush-and-fill periods. Mechanical coupling of CSF and vascular circulations is revealed from peak and latency phenomena during each cardiac cycle. Peak latencies on MRI-generated flow curves for CSF and cerebral blood flow are expressed as points over the cardiac cycle (0% to 100%).

Accordingly, in health, CSF flows along a regular pattern (Table 42.1). As systole begins, cerebral blood volume and ICP increase. The consequent flushing of cervical CSF relieves SAS pressure, enhancing jugular venous peak flow. Then, peak CSF flow (downward flushing) through the third ventricle–aqueduct helps equilibrate cerebral pressure. Following this flow sequence in systole, there are successive reverse phases during diastole for aqueduct refilling. CSF flushing phenomena in systole are precisely timed (see Table 42.1). Control data enable diagnosis of altered CSF-blood dynamic relationships in disease and aging.[129]

To delineate fluid dynamics in health versus neurodegeneration, it is advantageous to measure parameters in the aqueduct and SAS (C2–C3) concurrently. The ratio of cervical-aqueductal stroke volumes is ~15/1 in adults. A clinical impression suggests that cervical-aqueductal stroke volume ratio decreases with age. Variable compliance with disease in particular intracranial compartments helps assess distorted cervical-aqueductal stroke volumes. In deciding NPH shunts for imbalanced aqueductal-cervical functional relationships, the stroke volume ratio may be better than a single CSF compartment stroke volume.

CSF flow data from phase-contrast cine MRI facilitate noninvasive analysis of compliance. With aging, neurodegeneration, and CSF overloading, the CNS is less compliant. Brain therefore does not completely adjust to augmented pressure and volume. A compliance index (Ci), that is, change in volume/change in pressure, is calculated from volume changes (CSF and blood flows in a cardiac cycle) divided by the CSF pressure gradient (from CSF flow data). Ci values in NPH are lower than in brain atrophy or asymptomatic ventricular dilation. MRI flow analysis at the C2 SAS[130] is used with net blood flow (carotid and vertebral arteries; jugular veins) to assess brain Ci in NPH.

REGIONALLY INTERRUPTED CEREBROSPINAL FLUID FLOW IN NORMAL PRESSURE HYDROCEPHALUS

In chronic adult hydrocephalus,[131] CSF flow can be compromised at various regions along the neuraxis. To specify NPH state, one should elucidate differential impacts on brain and ventricular function caused by disrupted flow at sequential points: the Sylvian aqueduct, the basal cisterns, and the cortical SAS, which will be described in the following sections.

Sylvian Aqueduct

Cerebral aqueduct narrowing builds resistance to CSF flow through the brain interior, inducing an NPH-like syndrome. Late-onset idiopathic aqueductal stenosis usually has chronic onset; younger patients have headache, and older patients display NPH symptoms.[132] Endoscopic third ventriculostomy relieves late-onset idiopathic aqueductal stenosis,[132] especially when CSF outflow resistance is determined by test infusion. In animals and humans, late-onset idiopathic stenosis is associated with elevated venous pressure and greater collateral flow.[133]

Basal Cisterns

MRI-viewed basal cistern enlargement helps diagnose shunt-responsive idiopathic normal pressure hydrocephalus (iNPH).[134] Kaolin injection into animal basal cisterns[135] creates communicating hydrocephalus, allowing CSF outflow across the foramen of Luschka. CSF blockage in the cortical SAS permits modeling of extraventricular hydrocephalus. Tracking progression of basal cistern destabilization informs on evolution of early-life "decompensating" hydrocephalus to NPH.

Cortical Subarachnoid Space

Clinically important are the analyses of abnormal cortical CSF flow in NPH and AD.[136] Intrathecal kaolin in animals impedes orderly CSF flow in the SAS.[137] Kaolin given into cortical SAS induces backstream ventriculomegaly; the degree and rate of lateral ventricle expansion are less than that with cisternal injection.[135] More slowly dilating ventricles after cortical SAS injection mimic longer-onsetting NPH. In aging, NPH, and AD, structural changes in the SAS and arachnoid membrane increase impedance to CSF flow.[138,139]

CEREBROSPINAL FLUID FLOW REVERSAL IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Reversal of cranial-to-caudal CSF flow is measurable in the aqueduct and craniocervical junction. In health, CSF flow reversal occurs at the craniocervical junction, but not the aqueduct. Flow reversal occurs at both regions in iNPH. Thus spinal SAS CSF in iNPH patients is a source of CSF volume to support brain function (e.g., enhanced glymphatic clearance at night). A key question is whether the spinal SAS "source" actively produces CSF or if a CSF storage pool in the lower spinal SAS releases sequestered CSF to distribute cranially along a low resistance pathway to supra-aqueductal ventricles, and then transependymally (see Fig. 42.1). Gadobutrol and MRI delineate retrograde flow across the ependyma.[140] Shunting reduces the magnitude of "backward" flow to the lateral ventricles. These observations emphasize

TABLE 42.2 CSF Dynamics and Volume in Aging and Neurodegeneration

	Human Disease[a]			Rat Aging[b]		
	Normal	NPH	AD	3 mo	19 mo	30 mo
CSF formation rate (mL/min)	0.40	0.25	0.20	0.00121	0.00148	0.00065
CSF volume or space (mL)	150	300	250	0.156	0.196	0.308
CSF turnover rate (volumes/day)	4	1.2	1.2	11	10.8	3.0

AD, Alzheimer disease; *CSF,* cerebrospinal fluid; *NPH,* normal pressure hydrocephalus.
[a]CSF formation rate and volume is determined by the Masserman method.[40]
[b]CSF dynamics in rats was quantified by dilution of indicator perfused through the ventriculocisternal system.[150] CSF turnover rate = formation rate/volume.

CSF-brain adaptability in forging new flow pathways, including a spinal CSF source to compensate for hydrocephalus.

CEREBROSPINAL FLUID STROKE VOLUME ISSUES IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Better treatment of NPH, idiopathic and secondary, is driven by the burgeoning older adult population. New MRI biomarking emphasizes Sylvian fissure dilation and high-convexity tightness.[141] NPH categorization presents as *possible*, *likely*, and *definite* and therefore reflects intensifying stages. Evans index clinical analyses, normalized for ventricular dilation in healthy aging, demonstrate ~80% sensitivity for iNPH diagnosis.[142]

Hyperdynamic peak CSF flow velocity and lumbar CSF tapping corroborate iNPH diagnosis.[143] Maximum systolic flow through the Sylvian aqueduct usefully differentiates NPH from age-control patients.[144] Although CSF hydrodynamic data distinguish non-NPH from NPH,[145] the MRI parameters do not always predict a favorable response to shunting.[133]

Unstable CSF stroke volumes, increasing during early iNPH progression but then decreasing precipitously 3 to 4 years after onset, point to NPH irreversibility. Regressing central functions inform on the natural course of aqueductal dynamics in surgically untreated NPH. After NPH onset, aqueductal stroke volume typically increases for 18 months or longer.[146] Plateauing stroke volume occurs in progressing hyperdynamics; then a slight decline ensues for another 18 months before precipitously reduced aqueductal flow. Continually declining CSF flow in unshunted NPH, which decelerates rapidly, is caused by worsening ischemia and irreversible hydrocephalus.[146]

Pathophysiologic overlap among states of altered CSF dynamics creates a challenge when distinguishing NPH, AD, and NPH-AD and then managing the condition by shunting versus medical regimens. Although Aβ burden follows a continuum from aging to NPH to AD, the CSF hydrodynamics do not necessarily correlate. In a study of hydrodynamics and compliance, AD patients had aqueductal stroke volumes between NPH and controls.[133] When assessing NPH, the AD hydrodynamics in comorbid patients complicates stroke volume interpretation.

DWINDLING CEREBROSPINAL FLUID TURNOVER RATE IN AGING, NORMAL PRESSURE HYDROCEPHALUS, AND ALZHEIMER DISEASE

CSF *turnover rate* differs from formation rate and flow. Defined as *CSF formation rate* divided by *CSF volume*, the turnover rate measures the frequency of total CSF renewal. Senescence displays decreasing formation rate, even as the ventricular system adds volume. Advanced aging brings markedly curtailed CSF dynamics[40] and a diminished compensatory ability to respond to insults such as subarachnoid hemorrhage.[147] Impoverished CSF turnover combined with BBB breakdown are a double insult to the aging CNS.

The CSF system in NPH, as in aging and AD, produces less choroidal fluid[148] and has diminishing BCSFB homeostatic capabilities.[149] Ventriculomegaly is a prominent feature of NPH. Expanded ventricles contribute to a smaller calculated CSF turnover rate.[48,150] The volume of the SAS increases as AD progresses because of progressively deepening sulci. Incremented extracellular fluid volume adds stress on the choroid plexus management of CSF composition.[47]

CSF throughput, viewed as turnover rate, diminishes in senescence, NPH, and AD.[48] The turnover rate is lower in humans than in rats, and it declines substantially in both species during late life (Table 42.2). Attenuated CSF movement results in slower delivery of trophic substances to neurons (from the choroid plexus) and less-efficient volume transmission of signaling molecules to hormone targets in the brain. Sluggish CSF turnover also curtails cellular waste removal.

ALTERED CEREBROSPINAL FLUID AND BARRIER CLEARANCE SYSTEMS IN AGING AND NEURODEGENERATION

Brain catabolite removal avoids toxic buildup. CNS lacks true lymphatic capillaries. Still, three mechanisms clear waste materials: (1) BCSFB and BBB reabsorptive transporters (see Fig. 42.1), (2) CSF sink action (see Fig. 42.6), and (3) glymphatic ISF-CSF drainage.

Blood-CSF Barrier and Blood-Brain Barrier Reabsorptive Transporters

Transporters in the choroid plexus epithelium (apical membrane) and brain capillary endothelium (abluminal), respectively, actively remove organic anions from CSF and ISF. The potentially deleterious peptide, Aβ, is cleared by low-density lipoprotein receptor–related protein 1 (LRP1) at the BCSFB and BBB.[151,152] LRP1 density at the BBB (see Fig. 42.1) decreases in aging[153] and neurodegeneration,[154] thereby lessening clearance capacity. Faulty removal leads to amassing of Aβ, thereby impairing central fluid–balancing mechanisms and solute homeostasis. Contrariwise, LRP1 expression at the BCSFB *increases* in aging,[155] perhaps compensating for BBB decline.

Cerebrospinal Fluid Sink Action

CSF "sink action"[29,156] removes proteins/harmful catabolites from brain ISF. "Sink" clearance (see Fig. 42.6) results from a low concentration of organic solutes in nascent CSF secreted from the choroid plexus.[1] This sets up a concentration gradient for cortical macromolecules and catabolites that is directed from brain ISF into the ventricles and SAS. This *downhill* concentration gradient promotes net *diffusion* of harmful substances (from neural tissue into CSF bulk flow) that eventually convect with CSF to lymph and venous blood. CSF sink action attenuates with diminishing CSF formation[47] and transport (by choroid plexus[157]) in aging, NPH, and AD.

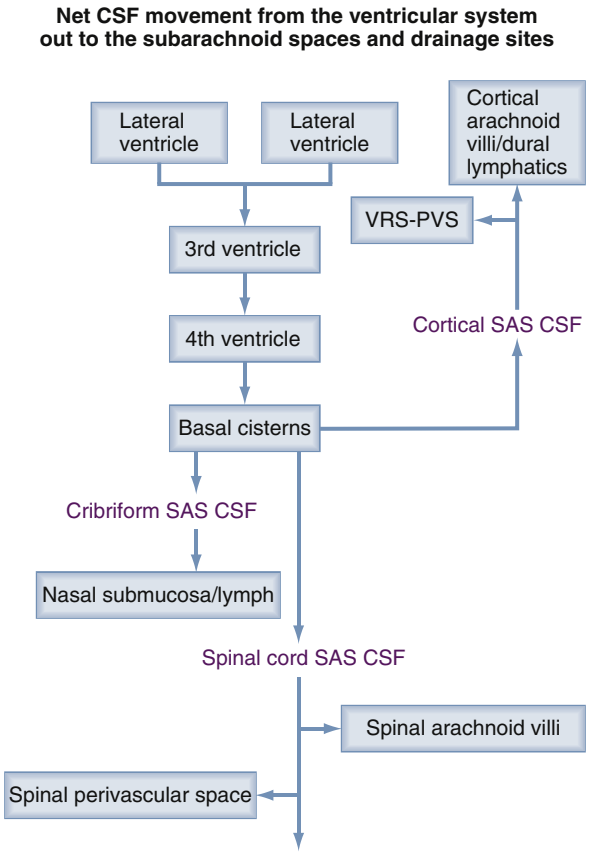

Figure 42.7. Net cerebrospinal fluid (CSF) flow from cerebral ventricles to the subarachnoid space (SAS) pathways and drainage sites in lymph/venous blood. CSF formed by the choroid plexus flows to basal cisterns and then outward to: (1) the cribriform plate–olfactory nerve for distribution to the nasal submucosa–cervical lymphatics, (2) the cortical SAS CSF containing Virchow-Robin spaces *(VRS)* as an entry point to the paravascular system *(PVS),* and (3) the spinal cord SAS with a paravascular system to receive materials from the subarachnoidal CSF to support spinal parenchyma. CSF flowing up over the cortical hemispheres accesses the VRS, arachnoid villi (clearance into venous sinuses), and lymphatic vessels in the dura mater (flow to cervical lymph). CSF streaming pathways in healthy humans (Fig. 42.7) are modified by disease in iNPH and Alzheimer disease. (*Modified from Johanson CE, Keep RF. Blending established and new perspectives on choroid plexus-CSF dynamics. In: Damkier HH, Balzer-Yost B, Praetorius J, eds. Role of the Choroid Plexus in Health and Disease. New York: Springer; 2020.*)

Glymphatic Interstitial Fluid–Cerebrospinal Fluid Drainage

Glymphatic drainage[158] is a pivotal excretory pathway that is particularly active at night. Glymphatic failure exacerbates neural diseases. The term *glymphatic* is from the word *glia* and the *lymphatic* system that it mimics. Glymphatics begins with a paravascular channel (astroglial "microtubes") containing SAS CSF, the inflow of which helps remove unneeded interstitial catabolites/proteins from the CNS (Fig. 42.7). Glymphatics work by CSF-ISF interactive motion (stimulated by Virchow-Robin arteriolar pulsatility) that flushes debris out of interstices back into the CSF, and then to dural venous blood and lymph glands.[8,121,159]

Aging impairs paravascular-interstitial clearance pathways.[160] Coupled with languishing CSF bulk flow in aging and chronic adult hydrocephalus,[161] this suppresses brain peptide clearance. Poorly eliminated interstitial Aβ caused by slower glymphatic flushing[162] promotes cortical Aβ deposition.[152]

Interstitial convection mixes with CSF influx to the brain,[121,163] initially at the Virchow-Robin spaces. Brisk mixing of the CSF and ISF percolations fosters neuronal viability. Attenuated interstitial mixing in senescence dams up CSF in ischemic parenchyma,[164] exacerbating iNPH. Deep white matter ischemia in iNPH augments interaction of stripped myelin with H_2O, thereby increasing resistance to ISF movement.[165] Impeded flow of CSF and ISF through the brain destabilizes the neuronal cytoskeleton relationship with tau. Consequently, synaptic purity and cognitive metrics falter[166] as ISF stagnates with retention of hyperphosphorylated-tau and Aβ.

TRANSLATIONAL NEUROSCIENCE TO FORTIFY CEREBROSPINAL FLUID–BRAIN DYNAMICS IN OLDER ADULT PATIENTS

Future pharmacomedical strategies[167] should include augmenting CSF formation to drive fluid through the CNS.[167] Improving CSF turnover rate in aging would stifle degeneration by curtailing oxidative stress on neurons. Interstitial well-being depends on balanced CSF formation, flow, and clearance. Medicinals/treatments are sought to enhance CSF movement into paravascular channels; this would likely speed up slackened glymphatic flow to the lymph nodes.[168] Expediting fluid movement through ventriculosubarachnoid spaces improves pressure-volume homeostasis by driving CSF through the cribriform plate[169] and arachnoid villi.

To stimulate dwindling fluid turnover in aging and AD, a promising target is transport interfaces.[170] In a diseased choroid plexus,[47] interstitial/capillary fibrosis[8,171] and immune deposits impede fluid movement across BCSFB.[172] Fibrous thickening of the pericapillary filtration membrane injures choroidal capillaries; macrophage clearance of extracellular waste (inflammatory exudates) at the BCSFB fades with excessive inflammation.[171] Preventing age-related deterioration at the blood-CSF interface protects the CSF-brain interior.

Another disruptor of ventricular hydrodynamics is hydrocephalus- and senescence-associated breakdown of ependyma.[173] High intraventricular pressure harms the structure of the ependymal CSF-brain interface that contains AQP4 channels for H_2O fluxes. Denuded ependyma and fibrillary (rosette) formation[174] impairs fluid movement between the ventricles and ISF. Especially helpful would be identification of factors that minimize deterioration of ependyma (see Fig. 42.1) in aging/neurodegeneration and chronic hydrocephalus.

Ischemic effects on arteries/arterioles[175,176] devastate downstream human capillaries in neurodegeneration.[173,176] This causes inefficient ISF generation/turnover by paravascular channels-astrocytes-glymphatics.[121] Cutting-edge analyses of transport/permeability of barriers[177] and metabolism of cerebral endothelium/astrocytes[178] inform on clinically important CNS fluid imbalances. Such research on fluids/barriers is essential because cognition is harmed by breaching of BBB, BCSFB, and CSF-brain interfaces (see Fig. 42.1).

Rebalancing CSF/brain disruptions entails identifying therapeutic targets at transport interfaces,[8] neurons/astrocytes,[178] and cerebrovasculature.[173,179] Investigating damage to human pericyte structure[180] and astrocyte foot AQP4/polarization[181,182] fosters understanding of ischemia-associated dementia. Correcting disordered solute-linked H_2O transport as well as blood flow reduction to brain/plexuses are key to restoring diminished fluid dynamics.

Improved MRI to assess the aging choroid plexus,[73] CSF-ISF hydrodynamics, and cerebral blood flow[183] facilitate understanding on how hydrocephalus, edema,[184] and impaired glymphatic drainage impair cognition. A new insight is that poststroke, the CSF influx accelerates into the brain along paravascular spaces,[184] evidently resulting from a favorable

hydrostatic gradient set up by diminished cerebral blood flow. Elucidating this process of CSF influx to the brain may provide a new therapeutic avenue to minimize edema following stroke.

CLINICAL CHALLENGES TO RECTIFY DISTORTED CEREBROSPINAL FLUID–INTERSTITIAL FLUID DYNAMICS IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

New NPH and NPH-AD hybrid research models characterize faulty CSF-brain metabolic relationships. Kaolin hydrocephalus modeling mimics accelerated aging and evolving iNPH pathology at the BBB, BCSFB, ependyma (see Fig. 42.1), and ISF.[135,161] Although kaolin experimentation is useful, analyses of human barrier tissue are potentially more clinically insightful and translatable.

How does altered CSF flow *couple* with distorted brain metabolism? Multiple mechanisms, including recruited alternate CSF outflow pathways, help cope with dissipative chronic hydrocephalus. As CSF turnover rate deteriorates, however, impaired metabolism worsens; eventually neurometabolic impairment decouples from CSF flow, so neuropathy does not improve after correcting fluid dynamics.[185] Therefore early identification of distorted metabolite levels by CSF and brain biomarking[185] will likely help thwart iNPH progression.

Healthy glymphatic flow, driven by CSF, is essential for staving off iNPH and AD. NPH treatment needs new agents[167] to adjust choroid plexus–CSF dynamics and promote ISF percolation[186] to lymphatic drainage sites (via CSF) outside the CNS. Better CSF biomarking[187] and shunt technology, along with drug-restored solute transport and aquaporin function at glymphatic targets, will likely improve iNPH flow disorders.

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