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The choroid plexus – cerebrospinal fluid system: Undervaluated pathway of neuroendocrine signaling into the brain

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The cerebrospinal fluid (CSF) is a major part of the extracellular fluid of the central nervous system. The function of the CSF and the tissue that secretes it, the choroid plexus (CP), has traditionally been thought as providing the brain with essential nutrients, removing products of neuronal activity of the central nervous system, and providing mechanical support for the brain's fragile cellular network. More recent studies suggest, however, that the CP and CSF system play a much more active role in the function of the central nervous system being a target, source and pathway for neuroendocrine signaling within the brain.

Key words: choroid plexus, CSF, neuroendocrine signaling

INTRODUCTION

Since the beginning of modern neuroscience, when the neuronal theory was developed specifying a nervous system composed of discrete nerve cells communicating through their synaptic contact, the concept of interneuronal communication in the central nervous system (CNS) has been revised several times. All these proposals have been quite different from one another, but they share as a common point of view the existence of another mode, besides synaptic transmission, for interneuronal communication in the CNS (Agnati et al. 1995). This complementary way of intercellular communication to classical synaptic transmission was named 'parasynaptic' (Schmitt 1984) or 'non-synaptic transmission' (Vizi and Labos 1991). In order to systematize the nomenclature, terms of wiring transmission and volume transmission (Fig. 1) have been suggested as the main conceptual categories of the intercellular communication in the CNS (Agnati et al. 1986). This concept of central signaling integrates the classical way of communication and the putative volume transmission pathways within the interstitial fluid (ISF) and cerebrospinal fluid (CSF) spaces (Agnati et al. 1992). This volume transmission is believed to involve both the short distance (diffusional) and the long-range (convective) movement of molecules within the CNS (Abbott 2004). Upon transport or secretion into the ventricles, molecules are conveyed by the CSF bulk flow to various regions of the brain and spinal cord (driven by hydrostatic pressure gradients between large-cavity CSF and dural venous sinus blood). Thus, the signaling molecules released into the ISF space within the brain tissue may act in an autocrine/paracrine manner, but may also move along the ventricular system and subarachnoid space with the CSF, and then exert distal, endocrine-like effects on target cells in the brain (Ferguson et al. 1991, Agnati et al. 1995).

Knigge and coauthors (1971) proposed the concept of humoral signals in the CSF in 1971. However it is not clear whether the presence of some substances in

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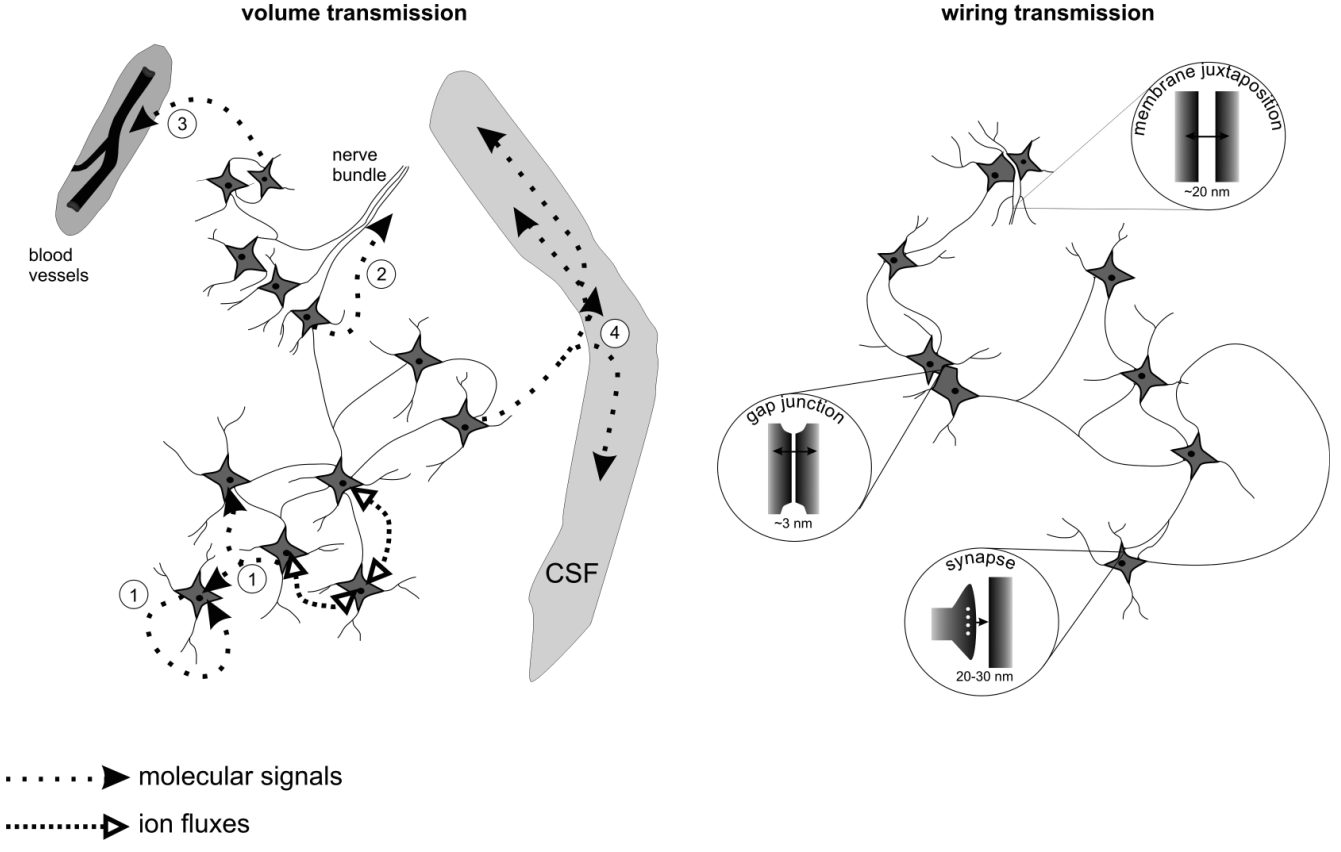

Fig. 1. Schematic drawing of the volume transmission and wire transmission types of intercellular communication in the CNS: In volume transmission signal diffuses within the brain extracellular fluid (ECF), therefore multiple, structurally often not well characterized ECF pathways participate in signaling within the brain: (1) simple diffusion (autocrine and paracrine type of signaling), (2) nerve bundle associated (preferential diffusion pathway), (3) perivascular space associated through the CSF (endocrine type of signaling, preferential diffusion pathway), (4) vector mediated (endocrine like type of signaling). The wiring transmission can be defined as intercellular communication occurring through a well defined connecting structure within neuronal and/or glial cell network. A structural link between two communicating cells determines relatively permanent and safe 1:1 link, while in the volume transmission signals deriving from a single source structure can reach several targets. Adapted from Agnati et al. (1995), modified.

the CSF reflects either a signal that uses the circulation of the CSF to distribute information far from its release site or a by-product that spills over in the ventricles after accomplishing its function in the brain. A few criteria must be met in order to demonstrate that the presence of substance constitutes a signal in the CSF and that this fluid compartment is the pathway for a diffusible or transported signal (Nicholson 1999). First, it should be shown that removal or replacement of the signaling substance results in a change in the response being controlled, and an assay should indicate changes of the signal level in relationship to the response. Second, the signaling molecule should have access to and enter the CSF and then be distributed within the brain by fluid movement. Third, the signal target represented by its receptors should be approachable by diffusion or by other system (Tricoire et al. 2002). Taking these criteria into account, there is already evidence for the existence of such signals in the CSF. For example, Pappenheimer (1983) showed that the CSF transfer from sleep-deprived goats made rats sleepy as well. Later, Silver and coauthors (1996) demonstrated in hamsters that suprachiasmatic nucleus transplants into the third ventricle restore circadian rhythms. For a number of physiological systems, there is good evidence that a diffusible signal is present in the CSF, originating not only from the brain but also from its periphery.

BASIC FEATURES OF THE CHOROID PLEXUS AND CEREBROSPINAL FLUID SYSTEM

The cerebrospinal fluid

To appreciate the potential of the CSF as a medium for carrying information, one must know the anatomy and physiology of the fluid spaces of the brain. The CSF is a major part of the extracellular fluid of the central nervous system, constantly produced by four choroid plexuses and in the ependyma, as well as in the capillary endothelium of the brain. About 10–30% of all CSF is extrachoroidal in origin, and is represented by bulk flow of the ISF from brain parenchyma into the ventricles and subarachnoid space (Cserr 1988). Studies on tracers injected into the CSF showed that the CSF and ISF exchange across both the bulk of ependyma covering the ventricles, and across the pial/glial layer at the surface of the brain within the subarachnoid space (Ghersi-Egea et al. 1996, Proescholdt et al. 2000). There is evidence that perivascular space (also called Virchow-Robin's space) is a route of the ISF circulation, from the CSF into the brain along arteries, and back out along veins (Rennels et al. 1985, Rennels et al. 1990, Zhang et al. 1992). In humans, approximately 600 ml of the CSF is formed each day, and this production has a tendency to show circadian variation, with a minimum production 30% of maximum values (12 ml/h) approximately at 06:00 PM and a nightly peak production approximately 02:00 AM of 42 ml/h (Nilsson et al. 1992b). Recently it has been demonstrated in sheep that the turnover rate of the CSF is also effected by day length, being slower in long days (approximately 71 μl/min) than in short days (approximately 170 μl/min) (Thiery et al. 2007).

In humans, there is about 150–270 ml of total volume of the CSF circulating but only about 25% are in the ventricles (Kohn 1991). The reminder fluid fills the basal cisterns and the subarachnoid space and flows around the spinal cord. The CSF moves from sites of formation, through the ventricles and subarachnoid spaces, to sites of reabsorption. Along the way, exchange with the ISF in the surrounding neuropil continually modifies the composition of solutes in the CSF (Johanson 2004). The fluid circulates from the lateral ventricles through the paired interventricular foramina of Monro into the third ventricle and thence by the Aqueduct of Sylvius into the fourth ventricle. From the fourth ventricle, the fluid passes into the various basal cisterns and then into the subarachnoid space through paired foramens of Luschka and foramen of Magendie. Probably, the flow of the CSF through the ventricular system involves both laminar and turbulent flow, the proportions of which differ from region to region (Takamata et al. 2001, Kurtcuoglu et al. 2007).

Compared to plasma ultrafiltrate, the CSF has a composition unique, containing higher concentrations of chloride, sodium and magnesium and lower concentrations of glucose, proteins, amino acids, uric acid, potassium, bicarbonate, calcium and phosphate. The CSF is not, however, an ultrafiltrate of the plasma, but is actively secreted by the CP. Active transports of ions through the epithelial layer serve as the driving force for the movement of water, and hence the formation of the CSF (Brown et al. 2004). Many substances have been detected in the CSF, some of which can penetrate the brain parenchyma as demonstrated by diffusion studies (Mufson et al. 1999) and by physiological and behavioral effects following their intracerebroventricular injections (Miller et al. 2002, Proescholdt et al. 2002). It should be noted that the composition of proteins and some other hormones in the CSF obtained from the lumbar puncture is different from that taken from ventricles. For example, lumbar CSF contains 2.2 times more albumin 2.6 times more IgG and only 0.7 times the transthyretin concentrations compared with the CSF collected from ventricles (Weisner and Bernhardt 1978).

The absorption of the CSF seems to be a dual process, rapid drainage through the arachnoid villi into the cranial venous sinuses, and to a lesser degree, a slow escape into the true lymphatic vessels by perineural course (Koh et al. 2005). Johnston and others (2007) has recently demonstrated in sheep that also the cavernous sinus veins may participate in the CSF absorption. The cavernous sinuses are paired venous channels in the dura located bilaterally on the cerebral surface of the basisphenoid bone, on both sides of the pituitary gland. In ungulates the cavernous sinus is converted, within their walls, into complex neurovascular structures containing numerous arteries (giving the main supply to the pituitary and the circle of Willis), cranial nerves (III, IV, VI, V) and many venous connections. The fact that the cavernous sinus is a place of the CSF absorption is very interesting since studies performed on a variety of species (pigs, sheep, rabbits, rats) indicate the existence of a local

system of transfer for substances from venous blood of the cavernous sinus into arterial blood supplying the brain and pituitary (Krzymowski et al. 1992, Grzegorzewski et al. 1995, 1997, Skipor et al. 1997, 2001, 2004, Einer-Jensen and Larsen 2000). It has been so far an overlooked pathway for distribution of humoral signals from one brain centre to other parts of the brain (Skipor and Einer-Jensen 2006).

The choroid plexus

In most reptiles, birds and mammals, the CP is present within each of the four ventricles of the brain. A few minor species specific differences exist, such as the absence of the CP in the third ventricle in sheep. In mammals, the CP from the lateral ventricles has a characteristic leaf-like structure floating in the CSF while the CP from the fourth ventricle rather resembles a bunch of vessels (Strazielle and Ghersi-Egea 2000). At microscopic level, the surface area of the CP is increased by numerous villi, each villus consisting of a single continuous layer of cuboidal epithelial cells overlying an extracellular stroma surrounding the vascular central core. Choroidal epithelial cells are derived from the ependymal lining of the ventricles and the blood vessels derives from a vascular fold of the pia mater termed 'tela choroidea'. The CP is highly vascularized leading to a good blood supply, that e.g. in rats is almost 10 times greater than the flow to the cerebral cortex (Szmydynger-Chodobska et al. 1994). The vascular core of the CP is a complex vascular network of relatively large venular-like capillaries with fenestrated endothelium. This facilitates the penetration of most small blood-born hydrophilic molecules across the capillary wall into the interstitial fluid of the CP. Ependymal cells possess numerous microvilli from the ventricle facing (apical side), and extensive infolding at blood facing (basolateral side), thus providing a large surface area for contact between epithelium and the CSF on one side and epithelium and the CP interstitial fluid on the other. The surface of microvilli in rat CP is about 75 cm^2 which is in the same range as in the total surface area (155 cm^2) of the capillaries of the blood brain barrier (Keep and Jones 1990a,b), therefore the difference in blood-brain barrier and blood-CSF barrier surface area is not so substantial. The cells of ependyma covering the CP like those of other secretory epithelia have polarized distribution of specific ion transporters so that the properties of their apical membrane differ from those of the basolateral membrane (Brown et al. 2004).

Many functions have been attributed to the CP, which depend primarily on the epithelial cells of this tissue. Beside the secretion of the CSF, the main functions are: regulation of access for chemical substances from blood to the CSF and synthesis and secretion of biologically active substances important for the functions of the CNS, such as plasma proteins, polypeptides, cytokines (Dickson et al. 1986, Nilsson et al. 1992a, Chodobski and Szmydynger-Chodobska 2001). Moreover, the CP is also a target of centrally released transmitters (Chodobski et al. 1998). About four decades ago Helen Cserr in her elegant review concerning physiology of the choroid plexus (Cserr 1971) wrote: "To the physiologist, whose interest is ultimately in function, one of the most fascinating aspects of the choroid plexuses concern their possible role in the overall activity of the central nervous system".

BARRIERS LIMITING AND REGULATING MOLECULAR EXCHANGE BETWEEN BLOOD AND BRAIN

Two barrier layers limit and regulate the exchange of molecules at the interface between the blood and brain tissue and its fluid spaces: the blood–brain barrier (BBB) between blood and interstitial fluid surrounding the neural tissue, and the blood–CSF barrier (BCSFB) that consists of two main anatomical components – the internally situated CP and the externally located arachnoid membrane. In contrast to the BBB, where brain capillaries sealed by tight junctions form a physical barrier between brain tissue and blood, the capillaries of the CP are fenestrated and it is the choroidal epithelium with their tight junctions which form what is known as the BCSFB. The CSF outside of the ventricles and the central canal of the spinal cord is located between the arachnoid and the pia mater. The arachnoid membrane is generally impermeable to hydrophilic substances, and its role in forming the BCSFB is largely passive. In the regions of circumventricular organs which participate in free exchange of substances between blood and ISF of the brain, there is no BBB. However, these organs are isolated from the CSF by tight junctions between the ependymal cells (Davson and Segal 1996). The BCSFB has three general barrier functions. First, the tight junctions between epithelial cells lining the choroid plexus form a physical

barrier to the diffusion of molecules, especially the large and hydrophilic ones, between blood and the CSF, and therefore paracellular diffusion (i.e. between cells) does not occur to any great extent. Second, the choroidal epithelial cells form an enzymatic barrier involved in uptake and degradation of many substances originating either in the brain or the blood, for example serotonin, noradrenalin and their metabolites. These cells express a lot of enzymes that degrade peptides including carboxy-, amino-, and endopeptidases (Smith et al. 2004). Also, many substances are sulphated or glucuro-conjugated by the enzymes when crossing the CP (Ghersi-Egea et al. 1994). Third, the choroidal epithelial cells contains a wide variety of specific and nonspecific transport systems, that both mediate entry of essential nutrients (glucose, amino acids) and regulatory substances into the brain, and also facilitate the elimination of xenobiotics and endogenous waste products from the CSF to the circulating blood (Kusuhara and Sugiyama 2004). Their polarized expression allows the efficient vectorial movement of their substrates through the BCSFB (Angelletti et al. 1997). Choroid plexus is an important delivery system for iron into the brain. The transfer of transferrin from blood to the CSF is higher than that of albumin, which may be due to the presence of transferrin receptors on the choroidal epithelial cells so that transferrin can be transported across the cells by a receptor-mediated process as well as by nonselective mechanisms (Moos and Morgan 2000). The main choroidal transporters which accept drugs and xenobiotics include the solute carrier (SLC) family and the ATP-binding cassette (ABC) carrier family (Davson and Segal 1996). Part of the ABC transporters is involved in multidrug resistance and two subfamilies are localized in choroidal epithelium: P glycoprotein (P-gp) and the multidrug resistance-associated proteins (MRP). However, as determined by immunohistochemical and drug-transport analysis of native CP and polarized epithelial cell cultures derived from neonatal rat CP, P-gp and MRP have opposite localization (Rao et al. 1999). P-gp is localized subapically while MRP basolaterally (Rao et al. 1999) what suggest their opposite transport directions (de Lange 2004).

The barrier restricts and regulates large molecular traffic (proteins), so that the CSF contains low protein concentration compared with blood plasma (Abbott 2004). Entry of particularly larger molecules with central action is provided by specific mechanisms for receptor- and adsorptive mediated transcytosis (Walsh et al. 1987, Banks et al. 1996, Chodobski and Szmydynger-Chodobska 2001).

SOURCE OF SIGNALING MOLECULES PRESENT IN THE CSF

There is much evidence for the presence of significant levels of neuroactive substances in the CSF as well as targets for these substances. In general, molecules present in the CSF originate from the blood plasma or the supraependymal nerve fibres (Mathew 1998), and may diffuse and/or be cleared (due to bulk flow of ISF) from the brain parenchyma as well as may be secreted by the CSF-contacting neurons (Liu et al. 1997, Vigh et al. 2004). Some molecules are synthesized in the choroid plexus and then secreted to the CSF (Chodobski and Szmydynger-Chodobska 2001).

Signaling molecules originating from the peripheral blood

Several peptides are thought to be actively transported by the choroidal epithelial cells to the CSF and most of the transported hormones evidently have, at least, a hypothalamic destination. For example, leptin synthesized mainly by adipose tissue is an important regulator of energy balance and major sites of its central action are localized in the hypothalamus, specifically in the arcuate, ventromedial and paraventricular nuclei. Leptin circulating in peripheral blood to reach its targets in hypothalamic nuclei has to pass through the BBB or BCSFB. High expression of short isoform of leptin receptor (OB-Ra) was found in the CP (Tartaglia et at. 1995, Devos et al. 1996). OB-Ra in the CP is not involved in the biological action of leptin but rather in the transport of hormone from blood to the CSF *via* a receptor-dependent transcytosis (Barr et al. 1999). The hypothesis that the CP plays a key role in regulating leptin entry into the CSF under physiological condition was supported by Zlokovic and coworkers (2000). They found rapid and high-affinity transport systems responsible for leptin uptake by rat hypothalamus and transport across the BCSFB. In contrast, in the same studies low-affinity carriers for leptin were found at the BBB in the CNS regions outside the hypothalamus. This suggests that circulating leptin is transported through the BCSFB and then carried *via* CSF bulk flow to its targets in the hypothala-

mus (Zlokovic et al. 2000). Interestingly, in male sheep, access of leptin to the CSF is quantitatively modulated by photoperiod, most probably involving control from the CP (Adams et al. 2006). In humans, clinical findings suggest that leptin resistance results from defective signaling, being a consequence of reduced uptake of leptin into the CSF (Caro et al. 1996).

Kondo and others (2006) identified a liver-derived protein complex as an essential coordinator of hibernation. This hibernation-specific protein complex (HPc) is synthesized in the liver. Authors found that in chipmunks, a hibernating rodent, the concentration of some specific components of HPc was significantly increased in the CSF before the onset of hibernation and peaked in the middle stage of hibernation when HPc concentration in the blood was the lowest. In animals unable to hibernate there was no upregulation of these proteins in the CSF. Additionally, some proteins from the complex are immunochemically localized in the cytoplasm of the choroid plexus epithelium, and the signal change with the hibernating statuses. Together, these observations strongly suggest that the CP plays a key role in the hormonal signaling of HPc for regulating brain functions for hibernation. Moreover, studies performed on ovariectomized ewes bearing intravaginal device releasing progesterone and subcutaneous estradiol implants demonstrated that long days increase progesterone and estradiol concentrations in the CSF while concentration in plasma remained constant (Thiery and Malpaux 2003, Thiery et al. 2003, 2006). Furthermore, the mechanism regulating this phenomenon involves the pineal gland (Thiery et al. 2006).

The choroid plexus – CSF system has been regarded as an important pathway for conveying prolactin (PRL) to the hypothalamus as a signal input that ultimately controls pituitary release (Smith et al. 2004). Soluble isoform of prolactin receptor (PRL-bp) participates in the transport of PRL from blood to the CSF or from the CSF to blood (Paut-Pagano et al. 1993). This explains the abundant PRL immunoreactive material present in the choroidal epithelial cells (Pi and Grattan 1998). Choroidal epithelial cells display high amounts of PRL receptor mRNA in pregnancy, with levels progressively rising as parturition approaches (Bakowska and Morrell 1997).

Receptor-mediated transport through the BBB has also been shown for insulin and insulin growth factor-1 (IGF-I) (Reinhard and Bondy 1994), data which suggests that a similar translocation system for these hormones exists in the CP epithelial cells, since localization of insulin receptors and IGF-1R and 2R were demonstrated in this tissue (Bondy et al. 1992, Kar et al. 1993).

Substances secreted into the CSF from the brain – signaling within the brain

It has been demonstrated in a number of mammalian species that gonadotropin-releasing hormone (GnRH) is present in the CSF (Miyake et al. 1980, Uemura et al. 1981, Vugt et al. 1985, Skinner et al. 1995, Williams et al. 1996). In sheep GnRH pulses in the CSF are simultaneous with peripheral luteinizing hormone (LH) pulses as well as accurately reflect the events occurring during LH surge (Skinner et al. 1995). The presence of GnRH in the CSF rises a question about its physiological function. It has been postulated that CSF-GnRH could act *via* an ultrashort-loop feedback system to regulate its own secretion. However, studies by Skinner and colleagues (1997) demonstrated that GnRH infused into the third ventricle in sheep had no effect on the mean interpulse interval, nadir, pulse amplitude or circulating level of systemic LH. These observations do not exclude that GnRH from the CSF has a behavioral effect. Studies by Caraty and coauthors (2002) demonstrated that GnRH is involved in the control of sexual receptivity in a ruminant species. Authors demonstrated that GnRH and estradiol acting in a sequential fashion allow the expression of estrous behavior, suggesting that the physiological role of the extended release of GnRH into the portal blood and CSF, comparing with LH, is to maintain sexual receptivity around the time of ovulation long after the triggering effect of estradiol.

Melatonin is another candidate as a signaling molecule carried by the CSF. First, melatonin is present in the ventricular system in sheep, particularly in the III ventricle in which its concentration is 20 times higher in the CSF than in blood (Shaw et al. 1989, Skinner and Malpaux 1999). Furthermore, melatonin enters the CSF through the pineal recess, as it was demonstrated in sheep (Tricoire et al. 2002). The target sites of melatonin action, at least in seasonal control of LH release, is localized in the premammilary hypothalamic area (Malpaux et al. 1998) that make it binding sites reachable by diffusion from the CSF (Tricoire et al. 2002).

A recent study using scintigraphy of radio-labeled melatonin in sheep has shown a rapid penetration of this hormone from the CSF to the diencephalic parenchyma bordering the third ventricle (Legros et al. 2006). Within the ventricular system, the rapid elimination of melatonin involved in the time-measuring-system (TMS) fits well with its functional requirement.

Substances synthesized in the choroid plexus

The CP regulate chemicals in the brain not only by limiting selectively the access of blood-borne substances to the CNS but also by serving as a unique source of essential molecules to the cerebral compartment. Numerous studies demonstrated the presence of protein and/or mRNA for a number of cytokines, growth factors and hormones in the CP, for example: interleukin-1β (Quan et al. 1998) interleukin-6 (Brochu et al. 1999), tumor necrosis factor-α (TNFα) (Tarlow et al. 1993), IGF-II (Bondy et al. 1992), nerve growth factor (NGF) (Timmusk et al. 1995), transforming growth factor-β (TGF-β) (Unsicker et al. 1991), vascular endothelial growth factor (VEGF) (Naito et al. 1995), transferrin (Tsutsumi et al. 1989), transthyretin (Dickson and Schreiber 1986) and vasopressin (Chodobski et al. 1997). Most of these substances have their own receptors in the CP (interleukin-1, TNFα, IGF, NGF, VEGF, TGFβ, vasopressin) and therefore may act in an autocrine/paracrine manner regulating choroidal hemodynamics and/or CSF formation (Chodobski and Szmydynger-Chodobska 2001). Just recently, Maharaj and others (2008) demonstrated that in adult mice both VEGF and TGF-β are involved in the regulation of CP endothelial cells stability, ependymal cells function, and periventricular permeability. On the other hand, substances synthesized by the CP and released into the CSF may also exert distal, endocrine-like effects on target cells in the brain due to the bulk flow of the CSF. For example, interleukin-1β in the CSF reaches its target receptors on the endothelia *via* perivascular volume transmission. Indeed, intracerebroventricular but not intravenous administration of this cytokine induces widespread vascular-mediated leukocyte (neutrophils and monocytes) infiltration and activation of astrocytes and microglia (Proescholdt et al. 2002).

Transthyretin (TTR), another protein synthesized in the choroidal epithelium, is the main thyroid hormones carrier protein in the CSF. In human CSF, approximately 80% of these hormones are bound to TTR. About 12% of protein newly synthesized by the CP *in vitro* and about 45% of protein secreted into the medium are composed by TTR (Dickson et al. 1986). It has been calculated that in humans only 3% of TTR in ventricular CSF and 10% of TTR in lumbar CSF are derived from blood (Reiber 2001). TTR is one component in the network of factors determining thyroid hormone delivery to the brain (Schreiber 2002). It has been suggested that TTR assists thyroxin (T4) transport from blood to the brain through the BCSFB and therefore TTR is critical to the supply of the CNS with T4. However, studies on TTR knockout mice showed that TTR is not essential for the transport of thyroid hormones to the brain but rather play an important role in sequestration of thyroid hormones within the brain parenchyma, as the brain thyroxin content is greatly reduced in TTR knockout mice (Palha et al. 1997). Just recently, Kassem and coworkers (2006) showed that binding T4 to TTR prevents its removal from the CSF, which supports the role of TTR in sequestration of thyroid hormones in the brain. Moreover, authors showed that TTR in rabbits significantly increases the uptake of T4 into the ependymal cells lining the ventricles, into the brain stem and into the hippocampus. In the last two structures the presence of ependymal layer potentiates the effect of TTR on T4 uptake. This is particularly interesting due to the fact that specialized ependymocytes lining the third ventricle express type II iodothyronine deiodinase (DIO 2) catalyzing the intracellular generation of triiodothyronine (T3) from T4 (Tu et al. 1997). It has been shown that local activation of the thyroid hormone in the mediobasal hypothalamus is critical for seasonal reproduction in birds (Yoshimura et al. 2003, Yasuo et al. 2005). Thyroid hormones are involved in the regulation of seasonal reproduction also in mammals. Thyroidectomy blocks transition into anestrus in sheep (Nicholls et al. 1988), and photopheriodic regulation of *Dio 2* is observed in hamsters and goats (Watanabe et al. 2004, Yasuo et al. 2006).

Another major protein from the CSF deserves attention too, the lipocalin-type prostaglandin D synthase (L-PGDS). It is synthesized by leptomeninges and CPs, and produce prostaglandin D2, one of the most potent sleep inducer (see Urade and Hayaishi 2000 for review). Interestingly, it is a good marker of CSF fistula and can be found in rhinorrhea and otorrhea (Kleine et al. 2000, Meco et al. 2003).

ROLE OF EPENDYMAL CELLS IN NEUROENDOCRINE SIGNALING

The ventricular system of the brain and the central canal of the spinal cord are covered with a single-layer of squamous, cuboidal, or columnar epithelial cells, called ependymocytes. The ependymal cells possess on their basal surface cytoplasmic processes that anchor them to the underlying nervous tissue. Most ependymocytes have cilia that project from its apical surface to the CSF. Depending on the presence or absence of cilia, the ependymal cells are classified as ciliated or non-ciliated cells. The ependymal cells are metabolically very active and are engaged in a variety of functions. Beating of ependymal cilia is required for normal CSF flow, concentration gradient formation of CSF guidance molecules and directional migration of neuroblasts (Sawamoto et al. 2006).

Besides the cilia, ependymocytes possess microvilli and blebs on their apical surface that are involved in the absorption and secretion of substances from and to the CSF (Gee et al. 1993). Ependymocytes lining the ventricles play a major role in regulating the microenvironment of nerve cells by preventing the re-entry of toxic and/or neuroactive substances from the CSF to the underlying neurophil (Del Bigio 1995). Since tight-junctions are lacking between ependymal cells lining the ventricular wall, not only CSF-contacting neurons but also subependymal neurons may be influenced by the molecules present in the CSF besides that of ISF of the brain tissue.

In the third ventricle, cells of the ependymal layer are not homogeneous and can be divided into ependymocytes and tanycytes (Fig. 2). The tanycytes line the floor and ventrolateral walls of the third ventricle between the rostral and caudal limits of the median eminence from the hypothalamus (Bruni 1974). Within this distribution tanycytes are regionalized into four subtypes (α1, α2, β1, β2), with α tanycytes regarded as the interface between the CSF and the neuropil in mediobasal hypothalamus, and β tanycytes contacting CSF and perivascular space of the portal capillaries in the median eminence (Rodriguez et al. 2005). There are functional differences

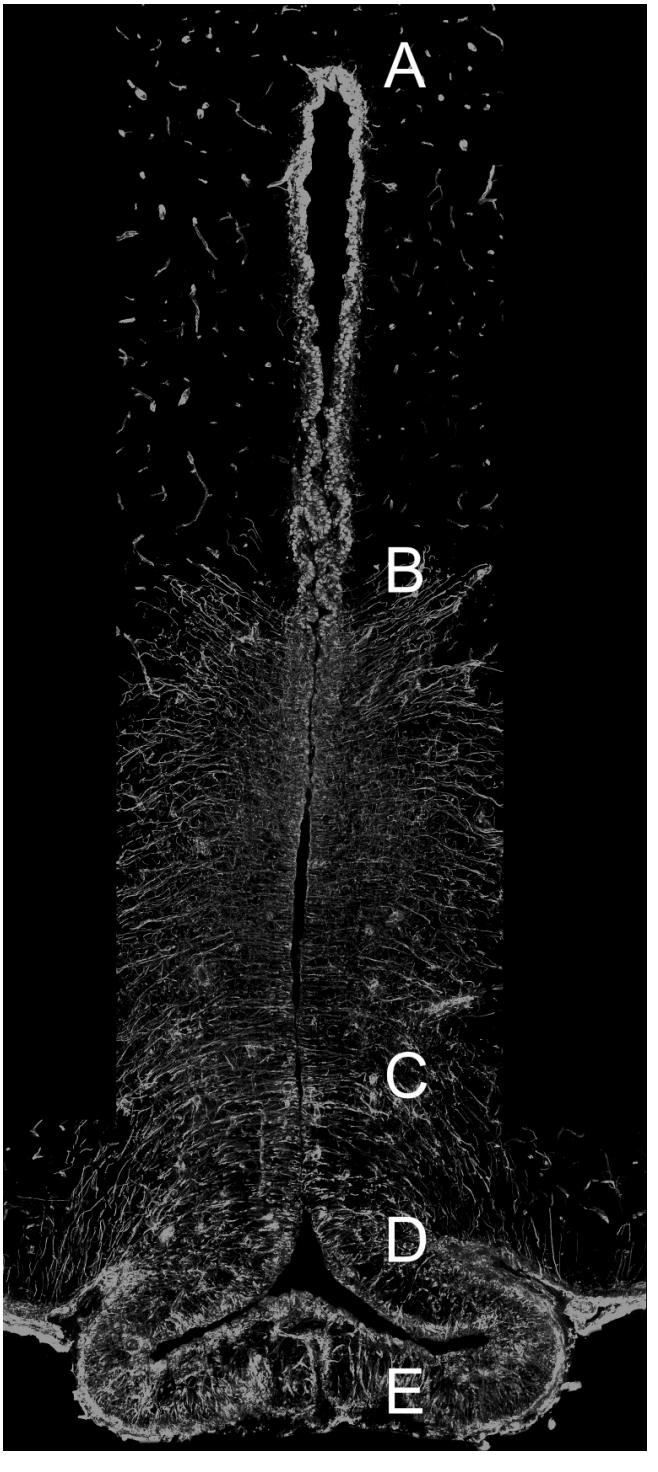

Fig. 2. Tanycytes in the hypothalamus in adult rats, immunostained with anti-vimentin, in coronal section. In the upper part, (A)–(B), anti-vimentin stains the ependymal cells of the third ventricle and the blood vessels scattered more laterally appear as points or lines according to their orientation related to the cut. More ventrally, (B)–(C), note the radial organization of the tanycytes feet ending in the wall of the III ventricle (α) and (C)–(D) note the curvilinear aspect of the most ventral tanycytes (β) around the median eminence, in (E). Gift from Mullier A., Dehouck B. and Prevot V., Development and Plasticity of the Postnatal Brain, Jean-Pierre Aubert Research Center Inserm U837 / University of Lille 2, Bâtiment Biserte 1 Place de Verdun, 59045 Lille Cedex, France.

between the four types of tanycytes. Types α1 and α2 of tanycytes do not have barrier properties, whereas type β1 forms a barrier between the arcuate nucleus and the median eminence, and type β2 between the CSF and the neuropil of the median eminence. Processes of tanycytes closely appose GnRH nerve terminals travelling down to the external layer of the median eminence. They also intervene between the nerve endings and the endothelial wall *via* the 'end feet' of tanycytes which essentially prevent direct access of the terminal to the portal vasculature (Prevot et al. 1999, Ugrumov et al. 1985).

The precise role of each group of tanycytes is not well known. However there is some evidence of transport between the CSF and the neuropil or the portal system (Peruzzo et al. 2004). It has been demonstrated that tanycytes absorb IGF from the CSF and transport it along their basal processes (Garcia-Segura et al. 1991). Tanycytes regulate GnRH release during the oestrous cycle by undergoing plastic changes that alternatively allow or prevent direct access of the GnRH nerve terminals to the portal vasculature (King and Letourneau 1994). For example, during the preovulatory surge of gonadotropins the end feet of tanycytes retract, allowing a significant fraction of GnRH nerve endings to directly contact the pericapillary space (Prevot et al. 1998, 1999). It has been demonstrated that the activation of erbB-1-mediated signaling in tanycytes results in plastic changes that, involving prostaglandin E_2 (PGE_2) and $TGF\beta_1$ as downstream effectors, mimic the morphological plasticity displayed by tanycytes during the hours encompassing the preovulatory surge of GnRH (Prevot et al. 2003). The importance of glial-neuronal-endothelial interactions in the control of GnRH secretion has been reviewed by Prevot (2002).

CONCLUSIONS

In conclusion, from this brief review we can propose a framework for future research bearing in mind that rapid increases in knowledge and the appearance of unexpected new concepts or methodologies may quickly invalidate our framework.

We can partition the major structures or systems under review into liquid compartments (CSF, ISF) and interfaces (CP, ependymal cells). Concerning liquid compartments, not only global concentration but also local changes and distribution of signaling molecules have to be taken into consideration. Indeed, sites of access to, or resorption from the compartments could explain the neuroendocrine impact of these molecules. For example, GnRH is measured in the ventral part of the third ventricle, but its concentration decreases when the distance from the median eminence increases (Skinner et al. 1995). Similarly, melatonin concentration is high in the pineal recess, slightly lower in the third ventricle (Skinner and Malpaux 1999) but almost undetectable in the cisterna magna (Rollag et al. 1977).

To study the distribution of signaling molecules by compartments implies the inclusion of hydrodynamic concept such as spatial and temporal dimension (Kurtcuoglu et al. 2007, Nilsson et al. 1992b), and the use of modern imaging methods such as magnetic resonance imaging or scintigraphy will be very helpful. To achieve that goal, large animal models such as sheep and goats, as well as human volunteers, are presently the best choice, while development of these methods of imaging for small laboratory animals will increase the field of investigation.

The functions of interfaces as barriers have already been extensively studied. However, they now have to be taken into consideration for their active physiological participation in the regulation of the dialogue between peripheral and humoral signaling molecules and the brain. This actually seems to be particularly true for CP which control the access of steroids, leptin or 'hibernating protein' in seasonal species (Adams et al. 2006, Kondo et al. 2006, Thiery et al. 2006). This could be extended in the future for the exchange of the molecules between CSF from the ventricular system and the brain parenchyma through ependymocytes and their differentiated elements, the tanycytes. Finally, the knowledge of compartments and interfaces will have to be incorporated in the systemic, integrative studies of neuroendocrine regulations.

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