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REVIEW ARTICLE

Light on a sensory interface linking the cerebrospinal fluid to motor circuits in vertebrates

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ABSTRACT

The cerebrospinal fluid (CSF) is circulating around the entire central nervous system (CNS). The main function of the CSF has been thought to insure the global homeostasis of the CNS. Recent evidence indicates that the CSF also dynamically conveys signals modulating the development and the activity of the nervous system. The later observation implies that cues from the CSF could act on neurons in the brain and the spinal cord via bordering receptor cells. Candidate neurons to enable such modulation are the cerebrospinal fluid-contacting neurons (CSF-cNs) that are located precisely at the interface between the CSF and neuronal circuits. The atypical apical extension of CSF-cNs bears a cluster of microvilli bathing in the CSF indicating putative sensory or secretory roles in relation with the CSF. In the brainstem and spinal cord, CSF-cNs have been described in over two hundred species by Kolmer and Agduhr, suggesting an important function within the spinal cord. However, the lack of specific markers and the difficulty to access CSF-cNs hampered their physiological investigation. The transient receptor potential channel PKD2L1 is a specific marker of spinal CSF-cNs in vertebrate species. The transparency of zebrafish at early stages eases the functional characterization of *pkd2l1*$^{+}$ CSF-cNs. Recent studies demonstrate that spinal CSF-cNs detect spinal curvature via the channel PKD2L1 and modulate locomotion and posture by projecting onto spinal interneurons and motor neurons *in vivo*. *In vitro* recordings demonstrated that spinal CSF-cNs are sensing pH variations mainly through ASIC channels, in combination with PKD2L1. Altogether, neurons contacting the CSF appear as a novel sensory modality enabling the detection of mechanical and chemical stimuli from the CSF and modulating the excitability of spinal circuits underlying locomotion and posture.

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1. Introduction

1.1. The interface between the cerebrospinal fluid and the central nervous system

The cerebrospinal fluid (CSF) refers to the fluid in the lumen of the neural tube after fusion. In mammals, this complex fluid is mainly secreted by the choroid plexus, vascularized epithelial cell structure, which develops in the lateral ventricles and the third and fourth ventricles of the brain (Dandy, 1918, 1919; O'Connell, 1970; Pollay & Curl, 1967; Welch, 1963, 1967). The CSF flows in the ventricles, the subarachnoid space around the brain and down the spinal cord in the central canal. The CSF has a high salt concentration, contains polypeptides passing through the blood–brain barrier but also encloses peptides and hundreds of proteins that are in a low concentration (200–700 µg protein/mL), including regulators of osmotic pressure, ion carriers, hormones binding proteins, regulators of lipid metabolism, components of the extracellular matrix and various enzymes and their regulators (Gato *et al.*, 2004; Parada, Gato, Aparicio, & Bueno, 2006; Parada, Gato, & Bueno, 2005; Ramirez-Boo *et al.*, 2012; Reiber & Peter, 2001; Swan *et al.*, 2009; Vio, Rodriguez, Yulis, Oliver, & Rodriguez, 2008; Yuan & Desiderio, 2005; Zappaterra *et al.*, 2007). Among the panel of chemical signals, the nerve growth factor (NGF) (Kasaian & Neet, 1989) or markers of the inflammatory responses such as the transforming growth factor alpha (TGF-α) (Van Setten, Edstrom, Stibler, Rasmussen, & Schultz, 1999) have been found. Hormones are also released into the CSF, including melatonin from pineal gland to the third ventricle (Skinner & Malpaux, 1999) and gonadotropin releasing hormone (GnRH) from the median eminence and possibly the *organum vasculosum* of the *lamina terminalis* (Skinner, Caraty, Malpaux, & Evans, 1997). CSF composition is dependent on the activity of surrounding brain tissue (Reiber, 2003; Skipor & Thiery, 2008) and on the activity of the subcommissural organ (SCO), a small gland located in the dorsocaudal region of the third ventricle. The SCO secretes Reissner's fiber (RF) complex that extends along the fourth ventricle and the central canal of the spinal cord (Chodobski & Szmydynger-Chodobska, 2001; Perez *et al.*, 1996; Vio *et al.*, 2008). The variations of these factors over time of the day and age of the individual have not been measured in healthy subjects. The modulatory roles of the

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CSF on the nervous system are also not well characterized and may be more complex than initially thought. Due to its location around the entire nervous system, anatomists originally postulated that the CSF could provide a hydromechanical protection of the nervous system (Davson, Kleeman, & Levin, 1962; Di Terlizzi & Platt, 2006; Iliff *et al.*, 2012). The CSF may also play a role in transport of nutrients (Agnati, Zoli, Stromberg, & Fuxe, 1995; Ferguson, Schweitzer, Bartlett, & Johnson, 1991; Mufson, Kroin, Sendera, & Sobreviela, 1999; Nicholson, 1999) and of the choroidal plexus secretion products to their site of action (Chodobski & Szmydynger-Chodobska, 2001). Recently, it has been shown that sleep results in the increase in convective exchange of CSF with interstitial fluid (Xie *et al.*, 2013). This exchange induces fluxes which increase the clearance of β-amyloid, endogenously present in interstitial space, suggesting that the CSF removes metabolic products insuring clearance of the interstitial fluid during sleep (Xie *et al.*, 2013). Recent studies also show evidence that cues from the CSF influence the formation of the central nervous system (CNS) during development as well as modulate cell proliferation and migration in the adult. Studies at the embryonic stages in the chick showed that embryonic CSF (e-CSF) promoted neuroepithelial stem cell survival and induced proliferation and neurogenesis on neuroepithelial cells (Gato *et al.*, 2005) and that this effect could in part be carried on by the Fibroblast Growth Factor 2 (FGF-2) (K. Martin & Groves, 2006). In rats, it has been shown that cortical cells were viable and proliferated in e-CSF (Miyan, Zendah, Mashayekhi, & Owen-Lynch, 2006) and that CSF provides a proliferative niche for neural progenitor cells with this effect attributable to the insulin-like growth factor (Igf2) (Lehtinen *et al.*, 2011). In the adult, CSF might also play a role in migration as shown with its implication on the guidance of neuroblasts from the lateral ventricles to the olfactory bulb by generating a chemorepulsive-factor gradient in the adult mouse brain (Sawamoto *et al.*, 2006). Bachy, Kozyraki, and Wassef (2008) showed that lipoproteins and exosome-like particles in the e-CSF strongly interact with neuropithelial cells via an endocytic process, which display regional specificity along the developing neural tube. These modulations by the CSF on its environment suggest a direct action via receptors interfacing the CSF and the CNS.

1.2. Modulatory role of the cerebrospinal fluid on the central nervous system

In addition to these roles, some studies have shown a modulatory function of the CSF content on the CNS. For instance, transferring CSF from sleep-deprived goats to cats induced deep sleep (Pappenheimer, Miller, & Goodrich, 1967). Similarly, intraventricular injections of CSF from fasted sheep induced feeding of satiated sheep (F. H. Martin, Seoane, & Baile, 1973). Also, by purifying the CSF of sleep-deprived cats, the fatty acid named cerebrodiene has been found particularly elevated (Lerner *et al.*, 1994) suggesting that CSF content reflects a given physiological state. Similarly, hypocretin-1 (also known as orexin-A) has been found in reduced amounts in the CSF of narcoleptic patients in human (Nishino *et al.*, 2001). All these studies suggest a strong and direct action of the CSF on the CNS indicating that its cues are integrated and transferred by the interface between the CSF and the CNS to the rest of the nervous system.

1.3. In the spinal cord, a proliferative niche surrounding the central canal

In the spinal cord, CSF flows in the central canal and is in direct contact with the cell populations bordering the canal. This heterogeneous region, which has mainly been investigated in rodents, is composed of several ependymal and subependymal cell types, which express specific markers and have specific morphologies and functions. In the ependymal layer are mostly found ependymocytes linked together by gap and zonula adherens junctions (Bruni & Reddy, 1987) and that mainly have two motile cilia (Alfaro-Cervello, Soriano-Navarro, Mirzadeh, Alvarez-Buylla, & Garcia-Verdugo, 2012), tanycytes sending projections to blood vessels (Bruni & Reddy, 1987; Seitz, Lohler, & Schwendemann, 1981), radial cells expressing the glial fibrillary acidic protein (GFAP) and radial cells expressing nestin ($GFAP^+$ or $Nestin^+$ radial cells) extending long radial processes to the pial surface (Alfaro-Cervello *et al.*, 2012; Hugnot & Franzen, 2011; Sabourin *et al.*, 2009). In the subependymal layer are located $GFAP^+$ cells and cells expressing the radial glia markers brain lipid-binding protein (BLBP) and CD15, cells thought to be a subtype of tanycytes (Hugnot & Franzen, 2011; Sabourin *et al.*, 2009). Among these ependymal and radial glial cells, can also interestingly be found a population of neurons named cerebrospinal fluid-contacting neurons (CSF-cNs) (Agduhr, 1922; Kolmer, 1921, 1931; Sabourin *et al.*, 2009; Stoeckel *et al.*, 2003; Vigh & Vigh-Teichmann, 1971). Altogether, these cells are commonly referred to as the neurogenic niche. This denomination comes from the neural stem cells properties that some of them have (Anderson & Waxman, 1985; Horner & Gage, 2000; Hugnot & Franzen, 2011; Johansson *et al.*, 1999; Sabelstrom *et al.*, 2013; Sabourin *et al.*, 2009), mostly the $GFAP^+$ ones (Sabourin *et al.*, 2009).

1.4. The anatomical identification of CSF-cNs

Cerebrospinal fluid-contacting neurons are a population of neurons located along the interface between the CNS and the CSF. CSF-cNs in direct contact with the CSF have the most favorable location and morphology to sense the content of the CSF, as well as to release compounds in the CSF, and relay this information to the rest of the CNS. CSF-cNs can be found throughout the brain in structures such as the SCO, the pineal gland, the hypophysis, the retina, the paraventricular organ among others (Vigh, Teichmann, & Aros, 1969; Vigh & Vigh-Teichmann, 1981, 1998; Vigh, Vigh-Teichmann, & Aros, 1970). CSF-cNs located in different organs differ in their morphology, the markers they express and the functions they might serve. This statement is formulated in reference to the work of Vigh and Vigh-Teichmann

who collected and put together a lot of information regarding the different types of morphologies in the CSF-cNs of different organs and different species. In birds, CSF-cNs of the paraventricular organ of the mediobasal hypothalamus have been found photosensitive and might be involved in the regulation of seasonal reproduction (Nakane, Shimmura, Abe, & Yoshimura, 2014). Also, in the rat mesencephalon near the midline of the ventral aqueduct and in the third and fourth ventricles, CSF-cNs express the cold sensation receptor channel TRPM8 (Du, Yang, Zhang, & Zeng, 2009) and might then be involved in pain sensation.

1.5. Identification of CSF-cNs in the spinal cord

Kolmer (1921) and Agduhr (1922) described in over 200 vertebrate species neurons lying around the central canal of the spinal cord using silver impregnation and Nissl staining. These cells were identified based on the atypical morphology of their soma and projection reaching the central canal. Kolmer (1921) referred to them as neurosensory cells and Agduhr (1922) as intraependymal neurons. Notably, they both reported that these cells exhibit an apical bulbous extension in the central canal and send basal axonal projections to other cells. Their observations suggested that CSF-cNs could compose a sensory organ (referred to as the parasagittal organ by Kolmer and sense organ by Agduhr) at the interface between the CSF and the CNS at the level of the spinal cord. Later on, CSF-cN peculiar morphology has further been investigated using electron microscopy (Vigh & Vigh-Teichmann, 1971, 1973). These studies report that CSF-cNs exhibit a dendritic terminal that protrudes into the lumen of the central canal but they further demonstrated that in some species this terminal possesses multiple microvilli, and, again according to the species considered, a motile kinocilium (Vigh & Vigh-Teichmann, 1973). Roberts and Clarke (1982) used backfilling staining with horseradish peroxidase to describe CSF-cNs in *Xenopus* as ciliated ependymal cells with cilia protruding into the lumen of the central canal and an axon projecting sagitally and rostrally to the brain. Since then, similar observations confirmed that CSF-cNs axon projected sagitally in the spinal cord (in *Xenopus* (Dale, Roberts, Ottersen, & Storm-Mathisen, 1987a, 1987b), in zebrafish (Djenoune *et al.*, 2017; Fidelin *et al.*, 2015; Wyart *et al.*, 2009) and in rat (Stoeckel *et al.*, 2003)). The development of immunohistochemistry on neurotransmitters enabled to demonstrate that CSF-cNs were GABAergic (rat: Barber, Vaughn, & Roberts, 1982; and xenopus: Dale *et al.*, 1987a, 1987b). The GABAergic phenotype of CSF-cNs became the main molecular criteria to define them coupled to their location surrounding the central canal contacting its lumen. Dale proposed to name them Kolmer–Agduhr cells (KAs) as a tribute to the pioneer work of the two scientists, nomenclature which is since then used in *Xenopus* and zebrafish (Dale *et al.*, 1987a, 1987b; Park, Shin, & Appel, 2004). Multiple terms have been used to refer to CSF-cNs: intra-ependymal neurons (Agduhr, 1922), ciliated ependymal cells (A. Roberts & Clarke, 1982), liquor contacting cells or neurons (Acerbo, Hellmann, & Gunturkun, 2003; Brodin *et al.*, 1990; Chiba & Oka, 1999; Dervan & Roberts, 2003; Kaduri, Magoul, Lescaudron, Campistron, & Calas, 1987; Megias, Alvarez-Otero, & Pombal, 2003; B. L. Roberts, Meredith, & Maslam, 1989; J. L. Schotland, Shupliakov, Grillner, & Brodin, 1996; Uematsu, Shirasaki, & Storm-Mathisen, 1993), KAs (Dale *et al.*, 1987a, 1987b; Park *et al.*, 2004) and CSF-cNs in the great majority of the literature. When the axon of CSF-cNs could be followed in the spinal cord, it appeared to project sagittally (Dale *et al.*, 1987a, 1987b; Djenoune *et al.*, 2017; Fidelin *et al.*, 2015; Stoeckel *et al.*, 2003; Wyart *et al.*, 2009). Often, the neuronal nature of CSF-cNs has been occluded due to the direction of the axonal projections relative to the section plane in transverse sections. Therefore, we cannot exclude that previous studies referring to these cells as ependymal cells were omitted here. We will use the general term spinal cerebrospinal fluid-contacting neurons or spinal CSF-cNs throughout this review.

2. Morphology, ultrastructure and localization of CSF-cNs in the spinal cord of vertebrates

2.1. Ultrastructure of CSF-cNs somata

Although all CSF-cNs bear an apical dendritic extension reaching the CSF, their morphology differs depending on the CNS region. For instance, the hypothalamic CSF-cNs bear one atypical non motile cilium ($9 \times 2+0$) and do not have microvilli (Vigh & Vigh-Teichmann, 1973, 1998). Spinal CSF-cNs have a peculiar morphology (Figure 1(A)). Their soma is located within the intra or the sub-ependymal layer of the central gelatinosa (referring to the area around and including the central canal, termed by Stilling and Wallach in 1824, cited by Lenhossék (1895)) (Agduhr, 1922; Kolmer, 1921, 1931; Nagatsu, Sakai, Yoshida, & Nagatsu, 1988; Vigh & Vigh-Teichmann, 1971, 1973, 1998; Vigh *et al.*, 1970; Vigh, Vigh-Teichmann, & Aros, 1974). CSF-cNs somata exhibit specific structural features when compared to neighboring cells. Indeed, among the dark stained ependymal cells, CSF-cNs are less-electron dense and send lightly stained processes coming from their somata located at the outer edge of the ependymal layer (Alfaro-Cervello *et al.*, 2012; Alibardi, 1990; Dale *et al.*, 1987b; Schueren & DeSantis, 1985). Their soma is generally round or ovoid (Barber *et al.*, 1982; Dale *et al.*, 1987a, 1987b; Djenoune *et al.*, 2017; Jaeger *et al.*, 1983; Shimosegawa *et al.*, 1986; Stoeckel *et al.*, 2003) but can also be triangular and fusiform (Barber *et al.*, 1982; Jaeger *et al.*, 1983; Shimosegawa *et al.*, 1986; Stoeckel *et al.*, 2003). Their nucleus is also mainly round to oval (Alfaro-Cervello *et al.*, 2012; Barber *et al.*, 1982; Marichal, Garcia, Radmilovich, Trujillo-Cenoz, & Russo, 2009; Schueren & DeSantis, 1985) and contains one or more nucleoli (Alfaro-Cervello *et al.*, 2012; Schueren & DeSantis, 1985). CSF-cNs somata are generally small with a diameter of around 10 µm (Barber *et al.*, 1982; Nagatsu *et al.*, 1988; Orts-Del'immagine *et al.*, 2014; Stoeckel *et al.*, 2003) but polygonal or rod-like ones can have a diameter of 13 to 28 µm (Shimosegawa *et al.*, 1986) and fusiform ones can be found up to 22 µm in length (Barber *et al.*, 1982). Compared to ependymocytes, they possess more microtubules and rough endoplasmic reticulum (RER) (Alfaro-Cervello

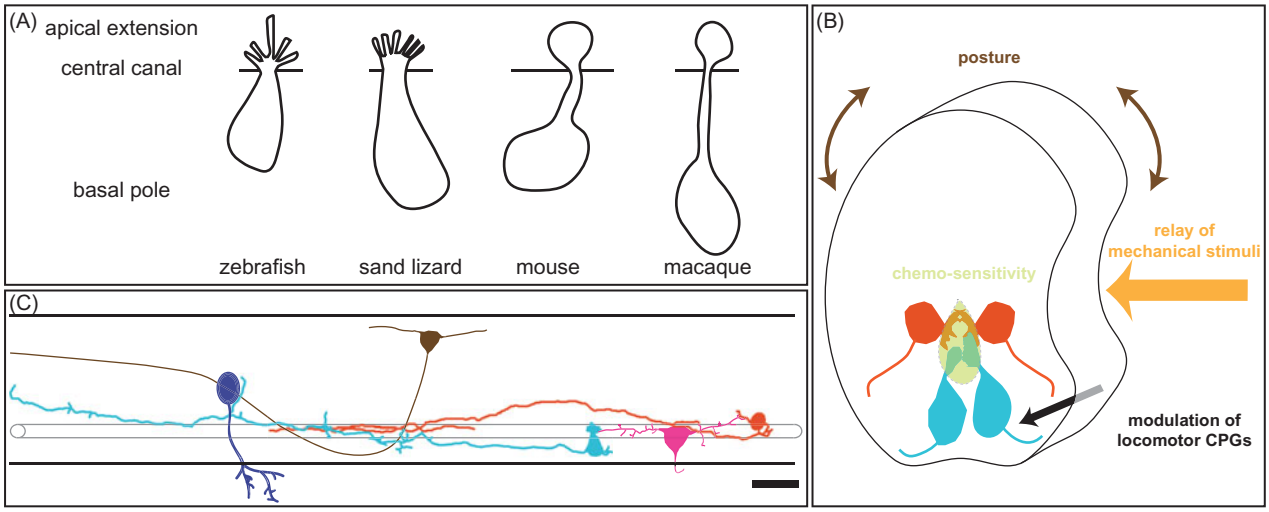

Figure 1. Graphical illustration of the morphological and functional properties of spinal CSF-cNs. (A) Spinal CSF-cNs possess a bulbous apical dendritic extension whose shape differs between species. In particular, the apical extension in anamniotes bears a multitude of microvilli while in amniotes the apical extension of CSF-cNs bears few microvilli. (B) Spinal CSF-cNs were shown to contact several classes of interneurons and motor neurons within the zebrafish spinal cord. Dorsal CSFcNs (first cell from the right) project onto V0-v (second cell from the right) when ventral CSF-cNs (third cell from the right) contact CaPs primary motor neurons (first cell from the left). Both populations of CSF-cNs project onto CoPA sensory interneurons (second cell from the left). (C) Spinal CSF-cNs are components of a sensory interface between the CSF and the CNS. CSF-cNs respond to active bending of the spinal cord, ensure the control of postural balance, provide input to spinal locomotor CPGs and might integrate cues form the CSF.

et al., 2012; Barber *et al.*, 1982; Schueren & DeSantis, 1985), and free ribosomes and dense core vesicles spread throughout their cytoplasm (Alfaro-Cervello *et al.*, 2012; Alibardi, 1990; Barber *et al.*, 1982; Marichal *et al.*, 2009) suggesting a high level of proteins synthesis. CSF-cNs cytoplasm lacks intermediate filaments and lipid droplets (Alfaro-Cervello *et al.*, 2012). CSF-cNs are linked to neighboring ependymal cells by apical zonulae adhaerens (Stoeckel *et al.*, 2003). Synaptic terminals can be observed at their abluminal side (Barber *et al.*, 1982; Jaeger *et al.*, 1983; J. L. Schotland *et al.*, 1996; Schueren & DeSantis, 1985; Vigh *et al.*, 1974; Vigh, Vigh-Teichmann, & Aros, 1977) terminals containing small, round and clear vesicles (LaMotte, 1987; Vigh *et al.*, 1977). They receive axo-somatic synaptic contacts (Alfaro-Cervello *et al.*, 2012; Djenoune *et al.*, 2017; Vigh, Vigh-Teichmann, Manzano e Silva, & van den Pol, 1983). Over the length of the spinal cord, CSF-cNs spread along the entire central canal but with a higher density at the thoracic level in rat (Shimosegawa *et al.*, 1986; Stoeckel *et al.*, 2003). Regarding their location relative to the central canal, rat CSF-cNs seem rather randomly distributed (Stoeckel *et al.*, 2003) while mouse CSF-cNs are mainly located dorsally and ventrally with fewer cells laterally (Orts-Del'immagine *et al.*, 2012). The density of CSF-cNs is higher in spinal cord than in brainstem (Orts-Del'immagine *et al.*, 2014).

2.2. An apical extension reaching the central canal

Spinal CSF-cNs bear at their apical surface an extension directed toward the central canal (Figure 1(A)), which lies in its lumen and expresses dendritic markers such as the microtubule-associated protein 2 (MAP2) (rat: Alonso, 1999; Kutna, Sevc, Gombalova, Matiasova, & Daxnerova, 2014; mouse: Orts-Del'immagine *et al.*, 2014). This structure has been referred to as a 'central body' (Vigh & Vigh-Teichmann, 1973; Vigh *et al.*, 1974), a 'dendritic process/terminal/ending' (Vigh & Vigh-Teichmann, 1973; Vigh *et al.*, 1974, 1977), 'brush border' (Dale *et al.*, 1987a), a 'bud' (Stoeckel *et al.*, 2003), or a 'bulb-like ending' (Jalalvand, Robertson, Wallen, Hill, & Grillner, 2014). We will refer to it as an apical dendritic extension here. This extension has the specificity of bearing a tuft of microvilli and in some species only a kinocilium, a canonical motile type of primary cilium. Microvilli are specialized plasma membrane extensions built around a parallel actin bundle (PAB), packed cluster of actin filaments (Bartles, 2000) held together by different sets of actin-bundling proteins (Bartles, 2000; Frolenkov, Belyantseva, Friedman, & Griffith, 2004). These actin bundles measure 1–5 µm in length and contain typically 20–25 actin filaments per bundle (Bartles, 2000; Heintzelman & Mooseker, 1992). On the contrary, the cilium is a membranous protrusion from the plasma membrane supported by a microtubule-based axoneme arising from the centriole during the G0/G1 state of the cell cycle (Alieva & Vorobjev, 2004). There are two types of cilia; primary cilia and motile ones. Primary cilia are non-motile and have a cytoskeleton consisting in nine doublets of microtubules ($9 \times 2+0$ structure). A primary cilium, found in most of the cells, is the sensory center of the cell that regulates cell proliferation and embryonic development. Motile cilia have nine doublets of microtubules as well but also an extra central doublet (two singlet microtubules in the center of the central ring) ($9 \times 2+2$). Notably in the sensory hair cells, the primary motile cilia are named kinocilia (Wersall, 1956). Kinocilia were first described by Wersall (1956) in hair cells, specialized mechanosensory receptors of the auditory and vestibular systems that convert head movements and sound waves into electrical signals (reviewed in Schwander, Kachar, & Muller, 2010). It became by extension the terminology used to designate the cilia of sensory cells (Flock & Duvall, 1965; Kindt, Finch, & Nicolson, 2012; Wersall, 1956). The kinocilium in auditory hair cells, contrary to vestibular ones,

is present at early developmental stages and regresses in mammals and birds while it remains in zebrafish and *Xenopus* (Denman-Johnson & Forge, 1999; Kikuchi & Hilding, 1966; Tanaka & Smith, 1978). In a similar manner, a kinocilium can be found in the apical extension of adult spinal CSF-cNs only in some species: in amphibians (Alibardi, 1990; Dale *et al.*, 1987b; Vigh & Vigh-Teichmann, 1998; Vigh, Vigh-Teichmann, Koritsanszky, & Aros, 1971), lamprey (J. L. Schotland *et al.*, 1996), chick (Schueren & DeSantis, 1985), carp (Vigh *et al.*, 1974), turtle (Trujillo-Cenoz, Fernandez, Radmilovich, Reali, & Russo, 2007; Vigh *et al.*, 1977) and possibly in rat (Marichal *et al.*, 2009; Stoeckel *et al.*, 2003). However, there is no consensus on this matter in rodents as cilia were located in other studies basally on the soma of CSF-cNs in mouse (Alfaro-Cervello *et al.*, 2012; Orts-Del'immagine *et al.*, 2014). This absence of kinocilium in the apical extension contacting the CSF seems to be shared by the rest of mammals investigated (such as rabbit in Leonhardt, 1967). The CSF-cNs apical bulbous dendritic extension bears multiple microvilli whose number varies across species (Jaeger *et al.*, 1983; LaMotte, 1987; Marichal *et al.*, 2009; Schueren & DeSantis, 1985; Vigh & Vigh-Teichmann, 1998; Vigh *et al.*, 1974, 1977; Figure 1(A)). For instance in *Xenopus*, CSF-cNs have been described as having a brush border consisting of long thin and numerous (sometimes more than 20) microvilli (Alibardi, 1990; Vigh & Vigh-Teichmann, 1998). Mammals CSF-cNs also have microvilli at their extension but less than in amphibians or teleost, as shown in mouse (Orts-Del'immagine *et al.*, 2012; Vigh *et al.*, 1983), in macaque (LaMotte, 1987), in opossum (Vigh *et al.*, 1983) and in rat (Jaeger *et al.*, 1983; Marichal *et al.*, 2009) although this point remains debated in rat (see Stoeckel *et al.*, 2003). The shape of the apical extension differs between species. Indeed, in anamniotes (fishes and frogs, incorrectly referred to as 'lower vertebrates'), microvilli are located at the apical pole of CSF-cNs somata. In amniotes (birds, reptiles and mammals), CSF-cNs extend at their apical pole a pod-like extension into the central canal resulting from a constriction of the apical pole bearing less microvilli. The observations from anatomy were not using any specific markers for labelling CSF-cNs. Consequently CSF-contacting terminals were distinguished from ependymal cells by their microvilli being longer and thicker than ependymal microvilli but shorter than kinocilia (Vigh *et al.*, 1974). In addition to microvilli, CSF-cNs apical bulbous extensions also exhibit subcellular structures that are representative of secretory cells. For instance, their processes enclose numerous vesicles and are rich in microtubules as shown for instance in rat (Jaeger *et al.*, 1983; Stoeckel *et al.*, 2003), in mouse (Alfaro-Cervello *et al.*, 2012; Vigh *et al.*, 1977), in guinea pig (Vigh *et al.*, 1983), in macaque (LaMotte, 1987), in chick (Schueren & DeSantis, 1985), in *Xenopus* (Alibardi, 1990) and in lamprey (J. L. Schotland *et al.*, 1996). CSF-cNs contact the lumen of the central canal by cytoplasmic blebs storing mitochondria, multivesicular bodies, dense granules, clear and dense core vesicles (Alibardi, 1990; Schueren & DeSantis, 1985). Rat CSF-cNs central and lateral processes contain pleomorphic vesicles of various sizes and granularity (Jaeger *et al.*, 1983). Regarding the junctions between CSF-cNs apical extensions and surrounding cells, at the sites where the microvilli enter the central canal, Vigh and collaborators observed desmosome-like junctions connecting the CSF-cNs processes with the neighboring ependymal cells (LaMotte, 1987; Vigh, Vigh-Teichmann, & Aros, 1971; Vigh *et al.*, 1974) although other authors observed zonula adhaerens between the apical extension and the ependymal cells (Stoeckel *et al.*, 2003) or both desmosomes and zonula adhaerens (LaMotte, 1987). From the work of Vigh and Vigh-Techmann, there is evidence that the apical extensions of CSF-cNs via their kinocilium may contact in some cases the RF (2004; Vigh *et al.*, 1970, Vigh, Vigh-Teichmann, & Aros, 1971). Kolmer (1921) suggested a connection in the receptor mechanism between the Reissner's fiber and the 'neurosensory cells' of the central canal. He hypothesized that this structure, dislocated by the movement of the spinal cord, could stimulate the terminals of the nerve cells. Nonetheless this is very difficult to establish without clear markers for CSF-cNs. It is though not unlikely that CSF-cNs cilia systematically contact the RF.

2.3. Description of CSF-cNs axonal projections

CSF-cNs axons have projections within the spinal cord lying in the ventral margin. However, their axonal distribution in the ventral spinal cord differs between species. Two main profiles have so far been reported. First, CSF-cNs axons run ventrolaterally to converge to a bilateral bundle called the centrosuperficial tract to form terminals on the ventral surface of the spinal cord. There, the fibers form neurohormonal nerve endings attached by hemidesmosomes to the basal lamina of the spinal cord facing the subarachnoidal space. Second, CSF-cNs axons project in an ipsilateral and ascending manner. In the turtle (*Emys orbicularis*), CSF-cN axons run to the ventrolateral surface of the spinal cord where they form terminal enlargements on the surface of the spinal cord (Vigh *et al.*, 1977). Interestingly, in the lamprey, CSF-cNs also extend processes to the ventral plexus (Christenson, Bongianni, Grillner, & Hokfelt, 1991; Jalalvand *et al.*, 2014; Megias *et al.*, 2003; Ochi & Hosoya, 1974; Vigh *et al.*, 2004) as well as to the ventrolateral margin where they display endfeet structures (Megias *et al.*, 2003; Vigh *et al.*, 1977) and reach the intraspinal stretch receptor called the edge cell (Christenson, Bongianni, et al., 1991; Jalalvand *et al.*, 2014). This axonal innervation allows the relay by CSF-cNs of information between the internal CSF, circulating within the central canal and contacted by the apical extension of the cells, and the external CSF, located in the subarachnoidal space reached by their axons. On the contrary, in other species such as the rat, CSF-cNs, axons run sagitally within a tight bundle running under the ependyma, inserted between basal poles of ependymal cells (Stoeckel *et al.*, 2003). They also extend more ventrally where they intermingle with myelinated axons of the corticospinal tract to eventually contact the walls of the ventral median fissure (Stoeckel *et al.*, 2003). Similarly, when single CSF-cNs were labeled *in vivo*, it was noticeable that their axons ascend ipsilaterally and run in the ventrolateral spinal cord (in xenopus and zebrafish: Dale *et al.*, 1987a, 1987b; Djenoune *et al.*, 2017; Fidelin *et al.*, 2015; Wyart *et al.*, 2009). Interestingly, in cat and macaque,

those two types of axonal projections are found. Indeed, their CSF-cNs can be traced to terminal fields along the ventral median fissure and the ventral lateral surface of the spinal cord (LaMotte, 1987). CSF-cNs axons contain large dense vesicles (Vigh *et al.*, 2004, 1977, 1983). The large granular vesicles found in the axons reaching the basal lamina of the external surface of the tissue in particular led to the idea that CSF-cNs may constitute a spinal neurosecretory system (Vigh *et al.*, 1977, 1983). CSF-cNs may be receptive to stimuli exerted by the internal (ventricular) CSF and capable of translating them into a neurosecretory output directed toward the external (subarachnoid) CSF (Vigh-Teichmann & Vigh, 1979, 1989; Vigh *et al.*, 1983, 2004). It also has to be noted that CSF-cNs express PSA-NCAM (Alonso, 1999; Bonfanti, Olive, Poulain, & Theodosis, 1992; Marichal *et al.*, 2009; Seki & Arai, 1993a, 1993b; Stoeckel *et al.*, 2003) and are not myelinated accordingly (rat: Stoeckel *et al.*, 2003; turtle: Vigh *et al.*, 1977).

3. Molecular characterization of spinal CSF-cNs

Several markers were found in CSF-cNs other than GABA. In the following part, we will review the different types of factors reported in spinal CSF-cNs.

3.1. The GABA as a general molecular marker of CSF-cNs

The gamma-aminobutyric acid (GABA) is considered as the main inhibitory neurotransmitter of the CNS. However, GABA is first excitatory at early stages of development and becomes inhibitory at later stages of neuronal differentiation (Boulenguez *et al.*, 2010; Sieghart, 1995; Stil *et al.*, 2009; Yamada *et al.*, 2004). GABA expression in CSF-cNs has been first reported in rat (Barber *et al.*, 1982). Since then, the expression of GABA in CSF-cNs, or expression of related enzymes such as glutamic acid decarboxylase (GAD) 65 and 67 isoforms or transporters such as the vesicular GABA transporter (VGAT), have been reported in many species: in rat (Barber *et al.*, 1982; Feldblum, Dumoulin, Anoal, Sandillon, & Privat, 1995; Kutna *et al.*, 2014; Mackie, Hughes, Maxwell, Tillakaratne, & Todd, 2003; Magoul, Onteniente, Geffard, & Calas, 1987; Stoeckel *et al.*, 2003), turtle (Reali, Fernandez, Radmilovich, Trujillo-Cenoz, & Russo, 2011), African clawed frog (Binor & Heathcote, 2001; Dale *et al.*, 1987a, 1987b), zebrafish (Bernhardt, Patel, Wilson, & Kuwada, 1992; Djenoune *et al.*, 2014; Higashijima, Mandel, & Fetcho, 2004; Higashijima, Schaefer, & Fetcho, 2004; S. C. Martin, Heinrich, & Sandell, 1998; Park *et al.*, 2004; Schafer, Kinzel, & Winkler, 2007; Shin, Poling, Park, & Appel, 2007; Wyart *et al.*, 2009; Yang, Rastegar, & Strahle, 2010; Yeo & Chitnis, 2007), eel (Dervan & Roberts, 2003; B. L. Roberts, Maslam, Scholten, & Smit, 1995), trout (B. L. Roberts *et al.*, 1995), carp (Uematsu *et al.*, 1993), dogfish (Sueiro, Carrera, Molist, Rodriguez-Moldes, & Anadon, 2004), amphioxus (Anadon, Adrio, & Rodriguez-Moldes, 1998), lampreys (Brodin *et al.*, 1990; Christenson, Alford, Grillner, & Hokfelt, 1991; Christenson, Bongianni, et al., 1991; Fernandez-Lopez *et al.*, 2012; Jalalvand *et al.*, 2014; Melendez-Ferro *et al.*, 2003; Robertson, Auclair, Menard, Grillner, & Dubuc, 2007; Rodicio, Villar-Cervino, Barreiro-Iglesias, & Anadon, 2008; Ruiz, Pombal, & Megias, 2004; J. L. Schotland *et al.*, 1996; Villar-Cervino, Holstein, Martinelli, Anadon, & Rodicio, 2008) and mouse (Feldblum *et al.*, 1995; Kaduri *et al.*, 1987; Orts-Del'immagine *et al.*, 2014). In addition, GABA seems expressed systematically in all CSF-cNs. The consistent GABAergic expression shared by all spinal CSF-cNs in many species became a way to identify them in combination with features reflecting their typical morphology. Interestingly, in rat, cells that appear to be CSF-cNs express $GABA_B$ receptor immunoreactivity (Margeta-Mitrovic, Mitrovic, Riley, Jan, & Basbaum, 1999). Moreover, looking at the distribution of GABAergic neurons in the rat spinal cord, Barber et al. (1982) identified two types of GAD-positive CSF-cNs with different somata shapes consistent with previous studies. These findings suggest that CSF-cNs consist in a heterogeneous population of neurons classified in at least two subtypes with specific morphological features. The hypothesis that CSF-cNs are heterogeneous is reinforced by the other markers observed in only subsets of these cells.

3.2. Other neurotransmitters found in spinal CSF-cNs

Other neurotransmitters were observed in CSF-cNs. For instance, *in situ* hybridization and immunohistochemistry for the vesicular transporter of glutamate (VGLUT) and glutamate itself in the lamprey spinal cord showed that all GABAergic CSF-cNs were glutamatergic (Fernandez-Lopez *et al.*, 2012). Glutamate, in addition to its essential metabolic role, is a major mediator of excitatory signals in the CNS and is involved in many physiologic and pathologic processes, such as excitatory synaptic transmission, synaptic plasticity, cell death, stroke, and chronic pain (Basbaum & Woolf, 1999; Mayer & Westbrook, 1987). The physiological relevance of the co-expression of GABA and glutamate in lamprey CSF-cNs remains to be determined. Nonetheless, this glutamatergic expression in CSF-cNs might be specific to lamprey. Indeed, in other species, glutamate has so far never been reported in CSF-cNs where its expression is found in other interneurons such as Rohon-Beard (Higashijima, Mandel, et al., 2004). Considering other markers of CSF-cNs, their expression appears restricted to only a subpopulation of the cells. For instance in the lamprey, looking at the distribution of another neurotransmitter, the glycine, in glutamatergic CSF-cNs, the authors observed that only some of them were also glycinergic (Fernandez-Lopez *et al.*, 2012). Similarly, comparing GABA and glycine expression in CSF-cNs, only ventral ones have been found expressing both markers (Villar-Cervino *et al.*, 2008), suggesting the existence of two molecularly distinct CSF-cN populations. Expression of glycine in a restricted subset of CSF-cNs might be specific to the agnathan though as glycine does not seem to be found in the CSF-cNs of the species where glycine spinal cord expression has been reported like zebrafish for instance (Higashijima, Mandel, et al., 2004).

3.3. Neuromodulator phenotypes of spinal CSF-cNs

In addition to neurotransmitters, several monoamines and neuropeptides can be found in CSF-cNs.

3.3.1. Catecholamines

Among monoamines, catecholamines are expressed in the CSF-cNs of salamander (Sims, 1977), garfish (Parent & Northcutt, 1982) and quail (Guglielmone & Panzica, 1985). Moreover, the enzyme responsible for catecholamine synthesis, the tyrosine hydroxylase (TH) can also be found in CSF-cNs of the African clawed frog (Heathcote & Chen, 1993), American bullfrog, Northern leopard frog (Chesler & Nicholson, 1985) and in chick (Wallace, Mondragon, Allgood, Hoffman, & Maez, 1987). Dopamine is found in CSF-cNs in multiple species: the lamprey (Barreiro-Iglesias, Villar-Cervino, Anadon, & Rodicio, 2008; McPherson & Kemnitz, 1994; Pierre, Mahouche, Suderevskaya, Reperant, & Ward, 1997; Pombal, El Manira, & Grillner, 1997; Rodicio *et al.*, 2008; J. Schotland et al., 1995; J. L. Schotland et al., 1996), ray (B. L. Roberts & Meredith, 1987), eel (B. L. Roberts *et al.*, 1989; B. L. Roberts *et al.*, 1995), chameleon (Bennis, Calas, Geffard, & Gamrani, 1990) and pigeon (Acerbo *et al.*, 2003). In these species, dopamine expression is mainly reported as ventral to the central canal in the floor plate (Acerbo *et al.*, 2003; Heathcote & Chen, 1993; B. L. Roberts *et al.*, 1995; Rodicio *et al.*, 2008). As reported for glycine, dopamine expression when compared to GABA is always found restricted to a subpopulation of GABAergic CSF-cNs (B. L. Roberts & Meredith, 1987; Rodicio *et al.*, 2008). The catecholamine expression pattern confirms the classification of CSF-cNs in at least two cell types.

3.3.2. Serotonin

In addition to catecholamines, some CSF-cNs express other monoamines in restricted species such as serotonin in the immature and adult salamander (Sims, 1977), in lamprey and hagfish (Ochi, Yamamoto, & Hosoya, 1979), in garfish (Parent & Northcutt, 1982), in spotted gar, in chick (Sako, Kojima, & Okado, 1986) and in zebrafish (Djenoune *et al.*, 2017; Montgomery, Wiggin, Rivera-Perez, Lillesaar, & Masino, 2016). As for previous markers, serotoninergic CSF-cNs were described ventral to the central canal (Ochi *et al.*, 1979; Sims, 1977) and restricted only to a subset of CSF-cNs (Djenoune *et al.*, 2017; Montgomery *et al.*, 2016).

3.3.3. Trace amines

Trace amines are structurally and metabolically related to monoamines but expressed in very small nanomolar concentrations (Borowsky *et al.*, 2001; Zucchi, Chiellini, Scanlan, & Grandy, 2006). The aromatic-L-amino-acid decarboxylase (AADC) trace amine has been reported in some rodents CSF-cNs (rat: Jaeger *et al.*, 1983; mouse and rat: Nagatsu *et al.*, 1988). Interestingly in these studies, immunocytochemistry for catecholamines and monoamines failed to show any signal. Concordantly, the authors did not find expression of TH, dopamine nor serotonin in AADC^{+} CSF-cNs. This might be explained by a difference of expression in mammals compared to anamniotes underlying species specific expression.

3.3.4. Neuropeptides

In addition to these classical neuromodulators, other molecules specific of neuronal cell types have been found in spinal CSF-cNs. Among them, somatostatin is the most common neuropeptide reported in these cells. Somatostatin has been found in CSF-cNs of lamprey (Buchanan, Brodin, Hokfelt, Van Dongen, & Grillner, 1987; Christenson Alford, Grillner, & Hokfelt, 1991; Jalalvand *et al.*, 2014; Lopez *et al.*, 2007), coho salmon (Yulis & Lederis, 1988b) and zebrafish (Djenoune *et al.*, 2017; Wyart *et al.*, 2009). In addition, urotensin II (UII)-like immunoreactivity and expression of neuropeptides of the UII family have also been described in CSF-cNs of several fish (Yulis & Lederis, 1986, 1988a, 1988b). Interestingly, the mutually exclusive expression patterns of somatostatin and UII or UII related peptides in CSF-cNs (Quan *et al.*, 2015; Yulis & Lederis, 1988b) confirm again the coexistence of at least two distinct subpopulations of CSF-cNs.

Among the peptides expressed by CSF-cNs, methionine–enkephalin–arginine–glycine–leucine (Met–Enk–Arg–Gly–Leu) is an endogenous opioid peptide identified from bovine adrenal chromaffin granules (Kilpatrick, Jones, Kojima, & Udenfriend, 1981). This peptide derives from Met-enkephalin which itself derives from proenkephalin. Shimosegawa *et al.* (1986) found that this opioid was expressed in rat CSF-cNs. Interestingly, the authors identified four types of CSF-cNs based on soma shape and axonal projections, suggesting that several subtypes of CSF-cNs with different morphological features coexist in the rat spinal cord. The functional relevance of CSF-cNs expressing opioids receptors agonists involved in pain transmission has to be determined.

One additional peptide, the vasointestinal peptide (VIP) mainly reported in the enteric system, has been found in CSF-cNs of mammals in rat and macaque (LaMotte, 1987).

3.3.5. Calcium binding proteins

Interestingly, among all the repertoires of factors expressed in CSF-cNs, the calcium binding proteins calbindin and calretinin have been found in spinal CSF-cNs of the lamprey (Megias *et al.*, 2003). Calcium binding proteins expression in CSF-cNs could be critical for the calcium modulation of the channel activity that will be mentioned in the next section.

4. Relevance of this sensory neuronal population to the spinal cord physiology

4.1. CSF-cNs as a sensory interface between the CSF and the CNS

The initial hypothesis of Kolmer and Agduhr regarding the function of CSF-cNs was that these cells were sensory neurons integrating cues from the CSF (1922, 1921, 1931). Erik Agduhr suggested that these neurosensory cells could perform regulatory functions within the spinal cord (1922).

Walter Kolmer suggested that the cells could have a mechanoreceptor function: by perceiving movement of the spinal column, they might connect via their axons to motoneurons thereby constituting a major component of an intraspinal proprioceptive sensory-motor loop (1922, 1921, 1931). Later, Vigh and Vigh-Teichmann who extensively characterized the ultrastructure of the CSF-cNs system, restated that CSF-cNs may be sensory because of their morphological resemblance to hair cells (Vigh & Vigh-Teichmann, 1971, 1973; Vigh *et al.*, 1977). A chemosensory hypothesis was strengthened by recent studies in mammals showing that CSF-cNs expressed the TRP channel PKD2L1 and that their firing was modulated by changes of extracellular pH (Huang *et al.*, 2006; Orts Del'Immagine *et al.*, 2012, 2015). CSF-cNs, through their apical extension, could therefore sense variation of CSF pH and relay this information to the rest of spinal circuits (Figure 1(B)). In addition, ATP in the CSF might regulate the activity of CSF-cNs. Indeed, CSF-cNs in the rat spinal cord express the specific subunit $P2X_2$ of ATP receptor P2X (Stoeckel *et al.*, 2003). Interestingly, the activity of the channel $P2X_2$ increases in response to an acidification (Dunn, Zhong, & Burnstock, 2001; Khakh, 2001; North & Surprenant, 2000). Thus, CSF-cNs $P2X_2$ receptors may detect changes in the concentration of ATP in the CSF, particularly under conditions of acidosis.

4.2. PKD2L1, a calcium-modulated channel expressed in CSF-cNs

Recent studies in mouse identified a channel as being specifically expressed in neurons located around the central canal contacting the CSF in the spinal cord (Huang *et al.*, 2006). This channel is called polycystic kidney disease 2 like 1 (PKD2L1) and has originally been identified for its role in sour taste in taste buds (Inada *et al.*, 2008; Ishii *et al.*, 2009; Ishimaru *et al.*, 2006, 2010; Kawaguchi *et al.*, 2010; Yu *et al.*, 2012; Zheng *et al.*, 2015). PKD2L1 belongs to the family of transient receptor potential (TRP) channels typically involved in detecting chemical, thermic and mechanical stimuli (Delmas, 2004, 2005; Nilius & Owsianik, 2011; Ramsey, Delling, & Clapham, 2006; Venkatachalam & Montell, 2007). Among the seven subfamilies of TRPs, PKD2L1 belongs to the transient receptor potential polycystin (TRPP) subfamily of Ca^{2+}-permeant ion channels composed of polycystic kidney disease (PKD) proteins and also named polycystins (Delmas, 2005; Ishimaru & Matsunami, 2009; Nilius, 2007; Sandford, Mulroy, & Foggensteiner, 1999). Sensory properties of PKD2L1 have been evoked in several studies that will be detailed below. PKD2L1 is a calcium-modulated (when over-expressed in xenopus oocytes as shown in Chen *et al.*, 1999) nonselective cation channel permeable to sodium, potassium and calcium ions. Upon rise of extracellular or intracellular calcium or under hypo-osmotic conditions, the channel shows large currents (Chen *et al.*, 1999; Delmas, 2005; Murakami *et al.*, 2005; Nauli, White, Hull, & Pearce, 2003). Upon discovery, PKD2L1 was shown to be expressed in CSF-cNs in the mouse spinal cord (Huang *et al.*, 2006). By FISH and IHC on coronal and sagittal sections of the spinal cord, the authors observed along the entire spinal cord distinct $PKD2L1^+$ cells with apical extension reaching the central canal. Since then, the generation of mice transgenic lines using pkd2l1 promoter provided insight on physiological properties of spinal CSF-cNs in mouse (Bushman, Ye, & Liman, 2015; Orts Del'Immagine *et al.*, 2012, 2015, 2014). Indeed, these studies showed that $PKD2L1^+$ spinal CSF-cNs fired action potentials in response to decreased extracellular pH (Bushman *et al.*, 2015; Huang *et al.*, 2006; Orts Del'Immagine *et al.*, 2012, 2015) as TRCs but do not show sustained inward proton current (Bushman *et al.*, 2015).

4.3. Secretory properties of CSF-cNs

In addition to a sensory function, CSF-cNs may have secretory properties. Based on their observations on ultrastructure, Vigh and Vigh-Teichmann proposed that the cells and their axons could constitute a neurosecretory system based on their axon endings containing synaptic vesicles and large dense vesicles. These terminals were found attached to the basal lamina of the external surface of the nervous tissue by hemidesmosomes where synaptic vesicles would be accumulated (Vigh & Vigh-Teichmann, 1971, 1973; Vigh *et al.*, 1977). CSF-cNs may therefore be receptive via their apical extension to stimuli exerted by the internal (ventricular) CSF circulating within the central canal, and capable of translating these cues into a neurosecretory output directed toward the external (subarachnoid) CSF reached by their axons. An alternative secretory function of CSF-cNs was proposed by Leonhardt (1967) to be located within the apical bulbous extension from which CSF-cNs would release their 'products' in the CSF within the central canal. Our characterization of large dense vesicles at the base of the apical extension of zebrafish CSF-cNs (Djenoune *et al.*, 2017) corroborates this hypothesis although it remains to be established whether and how these vesicles may be released in the CSF. Nonetheless, whether all spinal CSF-cNs share the same sensory properties is not clear. Recently, we demonstrated that CSF-cNs respond to passive and active bending of the spinal cord (Böhm *et al.*, 2016) and ensure the control of postural balance (Hubbard *et al.*, 2016; Figure 1(B)). Notably, we showed that dorsal CSF-cNs respond to active bending of the spinal cord selectively on the contracting side when dorsal contralateral and ventral cells remained mostly silent (Böhm *et al.*, 2016). These results suggest that the different populations of CSF-cNs could bear specific functional properties sustained by the pool of specific markers they possess or given their physiological context. They also suggest that CSF-cNs could constitute a mechanosensory system providing proprioceptive feedback to coordinate balance.

4.4. CSF-cNs role in the excitability of motor circuits

Activation of CSF-cNs can induce locomotion in zebrafish larvae (Wyart *et al.*, 2009) indicating that the cells could provide direct input to the spinal locomotor central patter generator. Recent studies from our lab reinforce this hypothesis (Djenoune *et al.*, 2017; Fidelin *et al.*, 2015; Hubbard *et al.*, 2016). We provided anatomical evidence for

projections from CSF-cNs onto three classes of premotor excitatory interneurons, V0-v, V3 and V2a interneurons (Djenoune *et al.*, 2017; Fidelin *et al.*, 2015; Figure 1(C)). These three classes are active during slow locomotion in larval zebrafish (Borowska *et al.*, 2013; Crone *et al.*, 2008; Dougherty & Kiehn, 2010a, 2010b; McLean, Fan, Higashijima, Hale, & Fetcho, 2007; McLean, Masino, Koh, Lindquist, & Fetcho, 2008; Menelaou, VanDunk, & McLean, 2014; Zhang *et al.*, 2008). Remarkably, this work reveals that CSF-cNs have an inhibitory action when they are stimulated during ongoing locomotion, while these cells induce delayed fictive swimming when activated at rest. We also demonstrated a direct connection between a subpopulation of CSF-cNs and CaPs motor neurons (Djenoune *et al.*, 2017; Hubbard *et al.*, 2016). These results indicate that CSF-cNs differently gate and tune the slow and fast locomotor central pattern generators and thereby control the occurrence and duration of locomotor events.

Whether the projections of CSF-cNs among spinal circuits are conserved across species is unknown. In lamprey, CSF-cNs send processes to the ventral plexus (Christenson, Bongianni, et al., 1991; Jalalvand *et al.*, 2014; Megias *et al.*, 2003; Ochi *et al.*, 1979; Vigh *et al.*, 2004) or the ventrolateral margin where they display endfeet structures (Megias *et al.*, 2003; Vigh *et al.*, 1977) innervation which allows the relay of information between the internal and external CSF. Lamprey CSF-cNs seem to make contact in the lateral plexus with the intraspinal stretch receptor called edge cells (Christenson, Alford, et al., 1991; Jalalvand *et al.*, 2014), which modulates the locomotor network (Grillner & Blomberg, 1984; Vinay *et al.*, 1996). This projection suggests that CSF-cNs may modulate locomotion by influencing edge cells and thus the locomotor-related sensory feedback. Whether this connectivity between CSF-cNs and premotor neurons or the modulatory role of CSF-cNs on locomotor CPGs is conserved in mammals remains to be determined.

Disclosure statement

No potential conflict of interest was reported by the authors.

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