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“Cooling and Cleaning” the brain- The role of CSF and the Paravascular System

“Arrefecimento e Limpeza” do cérebro - O papel do líquido cefalorraquidiano e do Sistema Perivascular

Margarita Beltran & Iype Cherian

College of Medical Sciences, Bharatpur, Nepal

Corresponding author – Iype Cherian; Email ID - drrajucherian@gmail.com

Abstract

Cerebrospinal fluid (CSF) transport is no longer believed to be on the conventional lines. The Virchow Robin (VR) spaces, otherwise termed the paravascular or perivascular pathway, which facilitate fluid transport between CSF and interstitial fluid (ISF), has kindled interest in a whole new array of studies. The aim of this paper is to explore novel hypotheses that account for the dynamic interaction of CSF and brain parenchyma in physiologic conditions, particularly, in “cooling and cleaning” the brain through the interstitial flow, and its involvement in the development of different CNS pathologies such as neurodegenerative disorders, like Alzheimers disease, postraumatic encephalopathy and Prion disease.

Keywords: virchow robin spaces, paravascular pathway, alzhiemers disease, chronic traumatic encephalopathy

Resumo

O transporte do Liquido Cefalorraquidiano (CSF) não é mais tido como convencional. Os espaços de Virchow Robin (VR), outrora designados como paravasculares ou perivasculares e que facilitavam o transporte entre o CSF e o fluido intersticial (ISF), têm despertado interesse num conjunto considerável de estudos emergentes. O objetivo deste trabalho é explorar novas hipóteses que demonstrem a interação dinâmica entre o CSF e o parênquima cerebral em condições fisiológicas, sobretudo no “arrefecimento e limpeza” do encéfalo através do líquido intersticial e o seu envolvimento no desenvolvimento de diferentes patologias do Sistema Nervoso Central (CNS) como as perturbações neuro-degenerativas, tais como a Doença de Alzheimer, encefalopatia pós-traumática e doença de Prion.

Palavras-chave: espaços virchow robin, paravascular, doença de alzheimer, encefalopatia traumática crónica

Introduction

The brain is a very active organ, consuming 20% of the oxygen and 25% of glucose of the body, despite only constituting 2-3% of the body weight (Alberts, Johnson,Lewis, Roberts & Walter, 2008). This high rate of metabolism, on almost a continuous rate, produce heat and metabolic bye-products that should be removed in order to maintain an adequate homeostasis in the brain. Regarding to this, a “cooling and cleaning” system is essential in order to bring the brain back to a basal state of temperature and chemical homeostasis. A failure to do this may result in physiological disturbances both in an acute and a chronic phase, leading to the development of different neurological pathologies. In our opinion, the dynamics of cerebrospinal fluid (CSF) in the cisterns and along paravascular spaces and its interaction with the interstitial fluid of the brain (ISF) constitutes both, the “cooling and cleaning” system of the brain. These functions would justify the fact that the CSF is produced in the ventricles and then pooled into the cisterns and that the entire CSF volume is changed 4-5 times in a day (Pardridge, 2011).

To understand the mechanism by which CSF in ventricular, subarachnoid space and paravascular spaces clear brain metabolites and avoid overheating of the brain it is essential to understand the dynamics of CSF and its interaction with the brain parenchyma. Recent studies indicate that CSF communicates with the brain interstitial fluid through the Virchow Robin Spaces (VRS) otherwise termed the paravascular spaces (Iliff et al., 2012, 2013), regulated mainly by a water channel, particularly aquaporin (AQP4), situated in the foot processes of perivascular astrocytes (Iliff et al., 2012 ; Nakada, 2014). This paravascular pathway was not studied in detail previously; but now the studies coming out point towards

the fact that this system is of paramount importance in the clearing of the metabolic waste (Iliff et al., 2012, 2013; Thrane et al., 2013; Xie et al., 2013) and probably it also plays a role in the cooling of the brain.

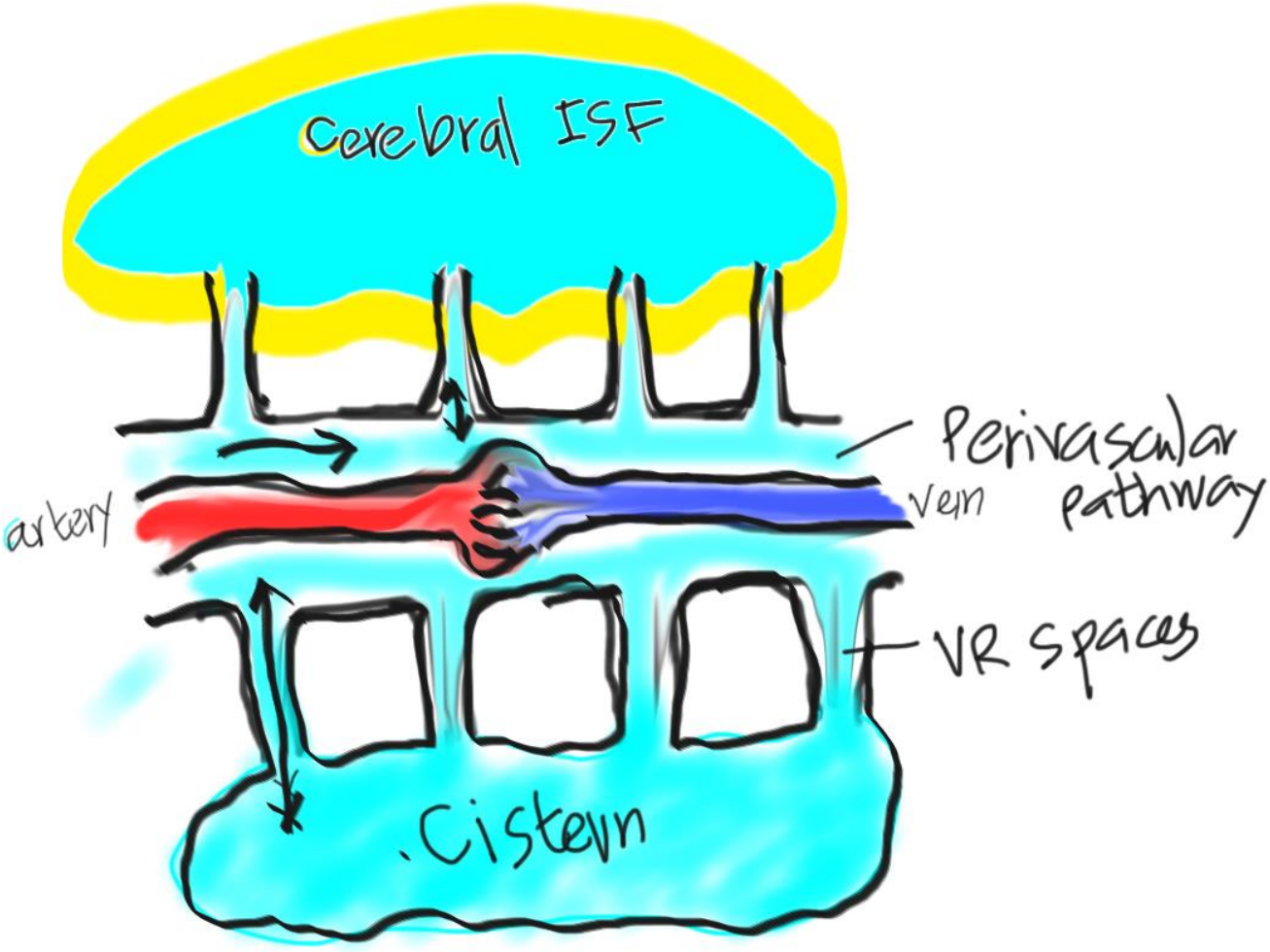

Figure 1 – The "Cleaning and cooling" model for interaction of CSF in the cisterns, the Virchow Robin spaces and the Cerebral ISF. The flow in the paravascular system from arterial to venous side (horizontal curved arrow), driven by arterial pulsations, acts as a heat sink as well as a sink for metabolic byeproducts. The paravascular system in in constant communication with the cerebral ISF (small bidirectional vertical arrow). This system will act as a metabolic sink which would take out the lactate or other metabolic byproducts and free radicals and transfer them to the venous system, thereby also helping to keep an intact blood-brain barrier whilst transferring the waste products into the venous system.

Cooling effect of CSF

The Brain is an intense producer of heat, releasing on average, 0.66 J every minute per gram of brain tissue (Yablonskiy, Ackerman, & Raichle, 2000). If not promptly removed, this heat generation and accumulation will lead to a continuous increase in local brain temperature. CSF in cisterns and moving and along paravascular spaces may be indeed, an intrinsic thermal regulatory mechanism likely providing a highly effective thermal exchange interface and regulation checkpoint in physiological conditions.

Considering the new concepts about dynamics of CSF through paravascular spaces (Iliff et al., 2012, 2013) and the vast CSF-cortical contact area of around 2300 cm^2 (Elias & Schwartz, 1969), and the 250 cm^2/g of brain contact surface through the perivascular spaces and the interstitial spaces (Raichle, 1983), broad thermal interaction between the CSF-brain and CSF - vessels must be inferred (Wang et al., 2014). Additionally, temperature buffering by CSF may be possible due to the close proximity between ethmoidal and sphenoidal sinuses and the suprasellar cistern. This cistern contains a large amount of CSF that enters into the highly metabolic areas of the deep brain (Berti, Mosconi, & Pupi, 2014) through the numerous paravascular channels along perforant arteries. The sphenoidal and ethmoidal sinuses are lined with mucous and they receive large amounts of moving air since they are part of the respiratory system. They add moisture to the air being breathed in, by evaporation of the mucus. This evaporation also causes the loss of latent heat producing an effect of cooling (much like having sweating person in the wind being cooled by the latent heat of evaporation of the sweat).

This cooling is conveyed by convection effect to the suprasellar cisterns. The CSF contained in the suprasellar cisterns is thus assumed to be cooled in a continuous fashion before

entering the deep brain through the Virchow Robin spaces driven by arterial pulsations. It should be noted that, when upper respiratory tract breathing is short-circuited there is an increase of the local temperature in the basal brain accompanied by a fast recuperation of baseline temperature after restitution of upper respiratory flow (Mariak, White, Lewko, Lyson, & Piekarski, 1999). At rest, venous blood temperature is approximately 0.3◦C higher than arterial blood (Yablonskiy, Ackerman, & Raichle, 2000). This could be due to the fact that the CSF in the paravascular pathway flows from the arterial to the venous system, thus acting as a heat sink and in turn heating up the venous blood by convenction.

It has been proven that activity in the brain causes an increase in blood flow that was supposed to be a way of bringing more oxygen to the region of activity until a disproportion between the blood flow (29% mean) as compared with oxygen consumption (mean, 5%) was found, regardless duration of the stimulus (Fox & Raichle, 1986). Clearing of the metabolic heat by the blood flow has been considered the reason for this disproportionate flow (Sukstanskii & Yablonskiy, 2006). However, considering the blood brain barrier and the paravascular system, we propose that this disproportionately high blood flow also increases the flow of CSF along the paravascular pathway, as this paravascular pathway is driven by cerebrovascular pulsation (Rennels, Blaumanis, & Grady, 1990; Iliff et al., 2012; Degennaro et al., 2013) allowing to a dissipation of metabolic heat in the active areas of the brain. The increased arterial blood flow reduces the paravascular space (Nakada, 2014), but increase the arterial pulsations and therefore drives more CSF flow achieving faster temperature buffering by a CSF that is constantly cooled by the interaction of breathing and air evaporation in the mucosal surface of the sinuses as described above.

It is interesting at this point to note that the cooling might occur much more in the sleep along with cleaning since it has been noted that during sleep, the aquaporin 4 channels allow much more CSF into the brain ISF (Xie et al., 2014). Recently, yawning has been proposed as a way to reduce the temperature in the brain (Massen, Dusch, Tonsi, & Gallup, 2014). Considering that when there is lack of sleep, there may be overheating of the brain. Yawning, which means more airflow, more evaporation and therefore more cooling of the basal CSF entering in the brain, could be a temporary way to cool the overheated brain in this circumstance and a warning sign that one should shut down the activity and go to sleep.

Cleaning

The brain also requires an efficient cleaning system to clear all the metabolic waste related to its high metabolic activity. The activity of the brain produces water and other byeproducts that need to be removed from the cerebral ISF in order to maintain a functional homeostasis. The paravascular system has already been proved to play an important role in the metabolic clearing of the brain (Iliff et al., 2012, 2013; Xie et al., 2014; Thrane et al., 2013). We would like to point out that this function is heavily dependent on the arterial-venous gradient/brain compliance and is likely to be dependent on the local temperature.

Recently, it has been shown that CSF from subarachnoid space enters the brain along para-vascular spaces mainly driven by arterial pulsatility from the para-arterial to the para-venous side (Iliff et al., 2012). During this passage exchange of fluids between paravascular spaces and ISF occurs bi-directionally (Agre,2006) driven by hydrostatic and osmotic forces (Bulat & Klarica, 2011) and this passage is controlled by AQP-4 present in the end foot of the perivascular astrocyte (Iliff et al., 2012 ; Papadopoulos & Verkman,

2013; Nakada, 2014). These exchanges may allow the transport and clearing of diluted metabolic waste from the interstitial space to the para-venular space. From there, they drain through the perineural sheaths of cranial or spinal nerves to systemic lymphatic, mainly around olfactory bulbs and cribiforme plate. Absortion of CSF through arachnoid granulations seems almost anecdotal (Nakada, 2014). Additionally, intraparenchymal vessels have a major influence in the dynamics of the paravascular spaces and therefore in the cleaning of the brain, by various mechanisms. Firstly, as it has already been said, the arterial pulsation drives forward the CSF in the surrounding paravascular space from the arterial side to the venous side, probably modulated by the breathing (Yamada et al., 2013). To do that, there has to be a pressure gradient between arteries and veins in the brain parenchyma and the brain compliance has to be intact. Additionally, capillaries actively participate in the osmotic and hydrostatic forces generated in the paravascular space with secretion and absorption of water molecules (Orešković & Klarica, 2010) and thus influencing indirectly, the exchange of fluid and molecules between CSF in the paravascular space and ISF. Finally, the vessels may actively transport certain substances from the paravascular space, even against osmotic gradients by co-transport with ions and glucose (Orešković & Klarica, 2010), participating directly in the cleaning process.

This cleaning is maximum in sleep (Xie et al., 2014) and lateral position (Orešković & Klarica, 2015) as it has been proved that during this time there are lower tissue resistance towards ISF flux and therefore cisternal CSF moves easily into the cerebral ISF through the paravascular spaces acting as a metabolic and heat sink. This is probably the reason why we are designed to sleep for a period of time during which time both these activities are at its height.

Interaction cooling and cleaning

The function of cleaning and cooling of the brain are highly dependent to each other because they share the same pathway: the CSF in the paravascular pathway. This fluid system, or fluid unit, is formed by all the uncolored liquids in and around the brain and spine (CSF in ventricles and subarachnoid space, the fluid along paravascular spaces, and interstitial fluid-intra and extracellular-). The interaction between those fluids components determine the homeostasis of brain microenvironment.

Locally, the temperature may have an essential role in the cleaning of the metabolic waste as it substantially affects water diffusion constant (Kozak et al., 2010) and solubility of molecules and therefore its transport through the AQP4. Furthermore, protein geometry, protein assembly or even protein expression may be affected with small temperature variations (Sukstanskii & Yablonskiy, 2006), which may be the difference between their abnormal accumulation or being cleaned in a physiological fashion.

Pathology of cleaning and cooling

Diverse neuronal disorders as for instance, cerebral amyloid angiopathy (CAA), Alzheimer disease (AD), Creutzfeld-Jacob disease (CJD) or chronic traumatic encephalopathy are characterized by deposit of abnormally folded proteins predominantly in the extracellular and paravascular space, and an abnormal clearing through the paravascular space as has been recently observed in all of them (Weller, 2001 ; Iliff et al., 2012 ; Thal, 2009 ; Nakada, 2014 ; Iliff et al., 2014 ; Faden & Loane, 2015 ; Xu et al., 2016 ; Thrane, Rangroo, & Nedergaard, 2014).

Deposition of insoluble prion protein (PrP) in Creutzfeldt-Jakob disease (CJD); beta-amyloid in Alzheimer's disease (Weller, 2001) amyloid peptides in amyloid angiopathy (Weller, Djuanda, Yow, & Carare, 2009; Kida, 2014) and

phosphorylated tau protein in chronic traumatic encephalopathy and after major traumatic brain injury are observed (Faden & Loane, 2015). These protein aggregates, or abnormally folded proteins, cannot leave the brain through AQP4 and accumulate in the brain interrupting the pathway for cleaning and cooling. We consider that, as temperature affects protein geometry and protein assembly (Sukstanskii & Yablonskiy, 2006) it is possible that the decrease on local thermal autoregulation would provoke or reinforce the disease process. Another fact that may corroborate this would be that the heat shock proteins, that are activated to induce heat tolerance, are increased in AD (Wilhelmus et al., 2006; Hamos et al., 1991).

Conclusion

The cooling and the cleaning, of a highly metabolic organ as the brain, are done by the passage of CSF through the paravascular spaces and its interaction with the ISF. Both functions, “cleaning and cooling”, are interdependent and at the same time are intimately related to the vascular situation and compliance of the brain. Pathology leading to the blockage of this pathway lead into a host of diseases characterized by accumulation of metabolic waste, particularly misfolded proteins, in the perivascular spaces. Research should be directed in the future to identify and correct this blockage and restore the cooling and the cleaning function of the brain.

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