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CELLULAR EDEMA AS A DETERMINING AGENT FOR THE PROMOTION OF INTRACRANIAL HYPERTENSION

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Abstract Intracranial Hypertension is a disease characterized by the reduction of Intracranial Pressure, causing an abrupt reduction of the Cerebral Blood Flow, which may result in the clinical picture of Cerebral Edema. This article presents, by means of integrative review, which are the possible etiological and pathogenic factors that may be related, emphatically, to the Cell Edema caused by Intracranial Hypertension. The objective of this study was to determine the pathogenesis related to the etiology of the aforementioned disease, as well as to approach its possible effects on the osmotic and electrolytic balances of the ion channels. For this review, searches in: Medline, PubMed, SciELO and Google Academic; having, as a search parameter, articles that were relevant to the subject addressed. The results obtained have the purpose of determining several pathogenies related to the etiologies of Intracranial Hypertension, thus concluding that it is an adversity still being understood by science.
Keywords: Ion Channels; Cytotoxic Edema; Electrolytes; Intracranial Hypertension; Osmolarity.

INTRODUCTION

Intracranial Hypertension (HI) is a brain condition in which the Intracranial Pressure (ICP) is above 15 mmHg, and may be related to several etiologies, such as the growth of lesions that occupy space in the cranial cavity; obstruction of CSF circulation, causing hydrocephalus; increased fluid in the interstitial and/or intracellular spaces of the brain; the Cerebral Edema itself and the engorgement of the encephalic microcirculation (JÚNIOR, CGC; COLLI, BO; DIAS, LAA, 1998), thus affecting several cerebral structures.

Thus, the Cerebral Edema, in order to emphasize them, can be influenced by the Cerebral Blood Flow (CBF), which is a rich complex of blood vessels, with an important division of functions, highlighting the conduction systems, resistance, exchange and reservoir (JÚNIOR, CGC; COLLI, BO; DIAS, LAA, 1998); there being, due to this constant self-regulation, the need to maintain a high metabolic demand in these cerebral vessels.

However, this high metabolism can be influenced by the Mean Arterial Pressure (MAP), which, if it is below 50 mmHg, can cause an abrupt decrease in FSC. This drop in blood flow contributes to intense cerebral vasodilation, which consequently results in the clinical picture of capillary vasoplegia, which can be interpreted as an obstruction in cerebral microcirculation (JÚNIOR, CGC; COLLI, BO; DIAS, LAA, 1998).

Thus, as a result of this obstruction in blood circulation, there is a breakdown of the blood-brain barrier, causing an increase in permeability in the capillary endothelium, which allows the passage of water and plasma proteins into the interstitial space (NEHRING, SM; TADI, P; TENNY, S., 2019), resulting in a large cellular swelling, that is, Cerebral Edema itself. Furthermore, this edema may be related to any type of stress that may be caused to the brain, such as hypoxia, neoplasia, trauma and metabolic imbalance, preventing the definition of a definitive etiology for such adversity (AYATA, C.; ROPPER, AH; 2002).

In this sense, there are 4 types of Cerebral Edema that can be caused by HI, namely: Vasogenic, Osmotic, Interstitial and Cellular/ Cytotoxic; in which, due to the fact that their physiopathologies are similar, that is, the decrease in CBF due to the decrease in MAP and the increase in ICP, there are differences between them due to the fact that the affected brain area is affected. However, in view of this, this article focused on Cerebral Cellular/ Cytotoxic Edema as a determining agent for the development of HI, as this is closely

related to the ion channels of neurons and astrocytes of the Central Nervous System, which, if the possibilities of imbalance in the osmolarity of the intracellular or extracellular media of these cells or of some adversity in their high metabolic demands, there is opportunity for the occurrences of ischemia and, consequently, in more severe cases of HI, cerebral hypoxia.

DEVELOPMENT

This article is an integrative approach to several other scientific projects that have contributed to the enrichment of neuroscience. To carry out this work, they were selected through the scientific research platforms: Medline, PubMed, SciELO and Google Scholar; several other articles, highlighting those in English and Portuguese, in order to promote a better foundation on the topic addressed. As a search parameter the following Keywords were used: Ionic Channels; Cytotoxic Edema; Electrolytes; Intracranial Hypertension; Osmolarity. The articles obtained had, as a selection criterion, data related to the theme: ´´Cellular Edema as a determining agent for the promotion of Intracranial Hypertension´´, discarding those that did not comply with the theme presented. There was no restriction as to when the particular article was published, so articles relevant to the subject from various eras were selected.

Likewise, Cerebral Cellular Edema or Cytotoxic Edema can be defined as the influx of cations, especially sodium, from the extracellular environment to the intracellular environment in neurons and astrocytes, through their ion channels. However, this influx of cations provides, for these neural cells, an efflux, that is, the exit of anions from the extracellular environment to the intracellular environment, resulting in the process of electrical neutrality by the balance of ionic charges, which, consequently, drives the entry of water into the intracellular environment, causing osmotic expansion of the neural cell (AYATA, C.; ROPPER, AH; 2002).

In this context, it is observed that, when this osmotic imbalance occurs in these cells, there is a change in their membrane surfaces, preventing ATP depletion due to a suppression of oxidative phosphorylation, resulting in a depletion of the remaining ATP reserves. Thus, if such an imbalance is not efficiently restored quickly, there is a compromise of metabolic homeostasis, since the osmotic balance of neural cells is achieved by the transport of sodium and potassium by ATPase enzymes, which are dependent on ATP (SWEENEY, MI; WAIZ, W.; YAGER, JY; et al., 1995).

Thus, with regard to the specific influx of cations to the cation channels, there is knowledge of two types of these channels that can contribute to the reduction of secondary injuries resulting from Cellular Edema, namely the Selective and Non-Selective Cation Channels (LIANG, D.; BHATTA, S.; GERZANICH, V.; et al., 2007). In conjunction with these channels, the Selective channels can be understood as allowing permeability to the passage of only one cation, such as sodium or potassium; while the Non-Selective have the characteristic of permeability of flow over any cations, which, consequently, in situations of osmotic imbalance or electrical neutrality of ionic charges, there is a contribution to the reduction of these secondary adverse effects of Cellular Cerebral Edema (SIMARD, JM; TARASOV, KV ; GERZANICH, V.; 2007).

Simultaneously with the approach to ion channels, as a result of their functional approach, there is a need to explain the main diversities of these channels in relation to the distribution of ions, highlighting: acid-sensitive ion channels, sulfonylurea receptor ion channels, transient receptor potential

channels, Na+ - K+ - 2Cl- cotransport channels, ionotropic glutamate receptor channels and, finally, water transport channels across biological membranes.

Thus, acid-sensitive ion channels can be understood as cation channels present in the Central and Peripheral Nervous Systems, acting through acidic pH, having their maximum activation at pH 6.2; since they are dependent on hydrogen and are inactive at alkaline pH, contributing to the flow of Na+2 and Ca+2, promoting an increase in cell excitability. In addition, it is noted that its activation can be caused by several factors, such as the aforementioned acidic pH, membrane stretching, arachidonic acid release, lactate production and/or the drop in extracellular Ca+2 in the cells. conditions in which swelling occurs, that is, cellular edema. (SIMARD, JM; TARASOV, KV; GERZANICH, V.; 2007).

In this sense, the sulfonylurea receptor ion channels are cation channels that carry out the conduction of all inorganic monovalent cations, namely sodium, potassium, cesium, lithium and rubidium; However, these channels are impermeable to cations. Ca+2 and Mg+2. As a result of this ionic selectivity, the SUR1 are expressed in the Central Nervous System only when there is a presentation of Ca+2 in the intracellular cytoplasmic environment, because, by the aggregation of Ca+2 in the presence of ATP, there is a blockade of these channels intracellularly; situation which is reversed when there is a depletion of ATP levels in cerebral edema, occurring, in these cases, an opening of the channels (SIMARD, JM; TARASOV, KV; GERZANICH, V.; 2007).

Continuously to the cation channels, the transient receptor potential channels have a high variation to intracellular stimuli, presenting, consequently, a wide possibility of activation factors, such as pH, redox state, osmolarity, elongation, voltage and Ca+2 (WOODARD, GE; SAGE, SO; ROSADO, JA; 2007). Furthermore, as a result of this Ca+2 activation factor, as soon as there is an increase in the level of this cation in the intracellular environment as a result of cerebral edema, these channels mediate the flow of Ca+2 into the cell, which contributes to, in addition to protecting the neural structure during adversity, the restoration of Ca2+ levels in the extracellular environment in the post-edema state; thus performing cellular protection in order to reduce oxidative stress (AARTS, MM; TYMIANSKI, M.; 2005).

Furthermore, with regard to Na+ - K+ - 2Cl- cotransport channels, are mediators of the aggregation coupler movement of Na and/or K with Cl, promoting involvement in ionic regulatory responses in epithelial cells of Glia cells, neurons, endothelium and Choroid Plexus. Such mediation of ionic aggregation is due to the fact that the driving force generated by the aggregation of Na/K-ATPase in the contribution of a concentration gradient favorable to Cl-, since, for the activation of this ion channel, it is necessary to position Na, K and Cl of the same cell membrane of these neural cells. In addition, this important maintenance of electrolyte levels is fundamental for the concentration of Na+2 in the intracellular environment, since the excessive influx of this cation due to decrease in intracellular Cl-, cellular hypertonic stress, increase in intracellular Ca+2 and stimulation of β-adrenergic receptors may be determining etiological factors for the result of a Cytotoxic Edema (LIANG, D.; BHATTA, S.; GERZANICH, V.; et al., 2007).

Simultaneously, the ionotropic glutamate receptor channels are involved in several aspects of the physiological and pathological activities of the Central Nervous System, since, when there is a resting membrane potential, this glutamate receptor channel is blocked by Mg+2, causing, during the period of membrane repolarization, to occur the

removal of this cation due to the conduction of Na, Ca and K (MORI, H.; MISHINA, M.; 1995). Thus, adversity occurs when the concentration of glutamate, which is normally around0.6 μM, rises suddenly for prolonged periods during a hypoxic situation, reaching values of 320 μM, which, consequently, as a result of uncontrolled depolarization, ends up resulting in an excessive removal of intracellular Mg+2, providing a influx, also uncontrolled, of Na+2 and Ca+2 into the intracellular environment, ending in a state of cerebral edema due to the high cellular excitotoxicity promoted by glutamate and the cellular injury itself (LIANG, D.; BHATTA, S.; GERZANICH, V.; et al., 2007).

This way, the channels transporting water across biological membranes(AQP´s) show a broad diversity according to their location and cell type found, dividing themselves into: AQP1 can be found in apical domains of epithelial cells of the Choroid Plexus, cell bodies of dorsal root ganglia and in the peripheral and central branches of primary afferent neurons; AQP3, AQP5 and AQP8 are found in astrocytes; AQP4, which are the most abundant, are expressed in the brain concomitantly in the astrocytic processes around blood vessels and ependymal cells facing capillaries and cerebrospinal fluid; and, finally, AQP9, which is located in midbrain dopaminergic neurons and mitochondria in cell bodies of tanycytes and astrocytes (LIANG, D.; BHATTA, S.; GERZANICH, V.; et al., 2007).Considering its main divisions, its functions are of passive conduction for the transport of water, considerably increasing the permeability of the cell membrane to water, which can already be related to its own etiology, because, in case of any stress situations oxidative and/or cellular, hypoxia or cerebral edema, there is an opening of these channels for the permeabilization of these channels so that a cellular metabolic and osmotic balance occurs, an example of which is AQP9, which allows, due to these mentioned adversities, that the mitochondria adjust to the extramitochondrial cytoplasm, which can certainly be a way of compensating for Cellular Edema.

FINAL CONSIDERATIONS

Therefore, it is observed that osmotic and electrolyte imbalances of ions, neural cells and ion channels can be caused by the various etiological factors of Intracranial Hypertension, such as the reduction in Mean Arterial Pressure, the reduction in Cerebral Blood Flow, hypoxia, neoplasia, trauma and others. Such adversities, due to the conditions of injuries that can be influenced: the cations, the influx of water, the cell excitability, the accumulation of free radicals, the concentration of hydrogen and the neutrality of ionic charges, are, these, definitive agents for the occurrence the engorgement of the encephalic microcirculation, which, consequently, contributes to the worsening of the metabolic disorders, thus ending Cerebral Edema and, consequently, Cellular Edema.

REFERENCES

AARTS, Michelle M.; TYMIANSKI, Michael. TRPM7 and ischemic CNS injury. **The Neuroscientist**, v. 11, n. 2, p. 116-123, 2005.

AYATA, Cenk; ROPPER, Allan H. Ischaemic brain oedema. **Journal of Clinical Neuroscience**, v. 9, n. 2, p. 113-124, 2002.

CARLOTTI JÚNIOR, Carlos G.; COLLI, Benedicto O.; DIAS, Luiz AA. Hipertensäo intracraniana. **Medicina (Ribeirão Preto)**, p. 552-62, 1998.

LIANG, Danny et al. Cytotoxic edema: mechanisms of pathological cell swelling. **Neurosurgical focus**, v. 22, n. 5, p. 1-9, 2007.

MORI, H.; MISHINA, M. Structure and function of the NMDA receptor channel. **Neuropharmacology**, v. 34, n. 10, p. 1219-1237, 1995.

NEHRING, Sara M.; TADI, Prasanna; TENNY, Steven. Cerebral Edema. **StatPearls Publishing**. 2019.

SIMARD, J. Marc; TARASOV, Kirill V.; GERZANICH, Volodymyr. Non-selective cation channels, transient receptor potential channels and ischemic stroke. **Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease**, v. 1772, n. 8, p. 947-957, 2007.

SWEENEY, Marva I. et al. Cellular mechanisms involved in brain ischemia. **Canadian journal of physiology and pharmacology**, v. 73, n. 11, p. 1525-1535, 1995.

WOODARD, Geoffrey E.; SAGE, Stewart O.; ROSADO, Juan A. Transient receptor potential channels and intracellular signaling. **International review of cytology**, v. 256, p. 35-67, 2007.