Is the Electrohypersensitive Patient's Headache a Variant of the Migraine Disease Mediated by TRPA1 Receptors?

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Abstract :
According to the French Agency for Food, Environmental and Occupational Health & Safety, electromagnetic hypersensitivity affects more than 3 million people in France, and headaches are a very frequent cause of complaint in electrohypersensitive patients, to the point of dominating the clinical picture. These headaches share characteristics with migraine pathology, and clinical improvement with anti-migraine therapy has led us to consider that the headache in the electrohypersensitive patient may be a variant of the migraine disease mediated by the TRPA1 receptor, which if confirmed, would offer effective therapeutic possibilities to relieve the electrohypersensitive patient.

Introduction :

Electromagnetic hypersensitivity is an environmental pathology that affects three to five percent of the population in France (1). In two-thirds of cases, women are affected by the disease by the age of 40. Clinical signs are dominated by neurological disorders ; more precisely by headaches in 98% of cases attributed to the presence of a source of non-ionising electromagnetic fields (2). The interrogation of patients sometimes also includes the triggering of headache with odours that can go as far as a symptomatology that etablishes the diagnosis of multiple chemical sensitivity confirmed by the QEESI (The Quick Environmental Exposure and Sensitivity Inventory) test (3).

Hypothesis :

The clinical presentation of these patients very closely resembles to the one of patients suffering from migraine triggered by odour or light (4). Having also noted the improvement in symptomatology with the use of a triptan or a prophylactic treatment for migraine, and after a review of the literature, we hypothesized that electrohypersensitive patient's headache is a variant of migraine disease in which the trigger is non-ionizing electromagnetic fields and the TRPA1 receptor is a key element in the process that may explain the findings.

It has been established that non-ionizing electromagnetic fields cause an increase in the concentration of intracellular free radicals in the human cell at sub-thermal thresholds (5,6). The mechanism of this increase, although debated, seems to be through the activation of

voltage gate calcium channels (VGCCs)(7,8) . This increase in free radicals at the level of nociceptive neurons and in particular the trigeminal nerve one's would activate the Transient Receptor Potential A1 (TRPA1) (9) which causes the neuron to secrete CGRP Calcitonin Gene Related Peptide (CGRP)(10) and inflammatory molecules such as substance p and neurokinin as well as the release of histamine (11). The CGRP will lead to arterial cerebral vasodilatation in the cerebral dura mater without action on the venous system, resulting in a migraine (12). In fact depending on the individual this is described as a brain fog and can go as far as a real migraine with vomiting and the whole typical procession.

TRPA1 belongs to the family of TRP (transient receptor potential) receptors (13) which are designed to detect changes in the surrounding environment. TRPA1 is directly sensitive to chemicals, particularly chlorine and wood smoke, as well as wasabi and menthol. It is also sensitive to cold and is activated by free radicals. This explains why at the cutaneous (14), pulmonary, oropharyngeal, digestive and urinary level it can be directly activated, reflecting the chemical sensitivity of patients who breathe smoke and have chest pain by releasing CGRP and inflammatory and painful substances. At the oropharyngeal level, the trigeminal nerve leads the information directly to the brain and triggers the "migraine" (15). In addition, when pulmonary TRPA1 receptors are activated they can cause heart rhythm disturbances (16,17,18).

Activation of TRPA1 and other receptors leads to a phenomenon of central sensitization which will result in an increasingly explosive reaction for a given stimulus, and in particular will facilitate the triggering of the reaction by different stimuli: light noise smell touch non ionizing electromagnetic fields and vibration creating what is known as a central sensitization syndrome (19,20,21).

It is even possible by repeatedly exposing rats to acrolein, a TRPA1 receptor agonist, to create a chronic migraine state, which is blocked by a pre-treatment with valproic acid, and whose effects are attenuated by sumatriptan (22).

Conclusion :
Thus, if our hypothesis is confirmed, since electrohypersensitivity headaches would be a variant of the migraine disease, this would finally give us a practical basis for work and offer effective therapeutic possibilities to relieve the electrohypersensitive patient.

Conflicts of Interest:
The authors declare no conflict of interest.

References :

1-ANSES (French Agency for Food, Environmental and Occupational Health & Safety). 2018.Hypersensibilité électromagnétique ou intolérance environnementale idiopathique

attribuée aux champs électromagnétiques. Avis de l'ANSES Rapport d'expertise collective. Available online: https://www.anses.fr/fr/system/files/AP2011SA0150Ra.pdf

2-Belpomme, D, Irigaray, P, 2020. Electrohypersensitivity as a Newly Identified and Characterized Neurologic Pathological Disorder: How to Diagnose, Treat, and Prevent It [WWW Document]. International journal of molecular sciences. https://doi.org/10.3390/ijms21061915

3-Miller, C, Prihoda, T, 1999. The Environmental Exposure and Sensitivity Inventory (EESI): A Standardized Approach for Measuring Chemical Intolerances for Research and Clinical Applications [WWW Document]. Toxicology and industrial health. https://doi.org/10.1177/074823379901500311

4-The International Classification of Headache Disorders, 3rd edition (beta version), 2013. . Cephalalgia 33, 629–808. https://doi.org/10.1177/0333102413485658

5-Choi, J., Min, K., Jeon, S., Kim, N., Pack, J.-K., Song, K., 2020. Continuous Exposure to 1.7 GHz LTE Electromagnetic Fields Increases Intracellular Reactive Oxygen Species to Decrease Human Cell Proliferation and Induce Senescence. Scientific Reports 10. https://doi.org/10.1038/s41598-020-65732-4

6-Belpomme. D., Hardell, L., Belyaev, I., Burgio, E., Carpenter. D, 2018. Thermal and Non-Thermal Health Effects of Low Intensity Non-Ionizing Radiation: An International Perspective [WWW Document]. Environmental pollution (Barking, Essex : 1987). https://doi.org/10.1016/j.envpol.2018.07.019

7-Sharma, S., Wu, S.-Y., Jimenez, H., Xing, F., Zhu, D., Liu, Y., Wu, K., Tyagi, A., Zhao, D., Lo, H.-W., Metheny-Barlow, L., Sun, P., Bourland, J.D., Chan, M.D., Thomas, A., Barbault, A., D'Agostino, R.B., Whitlow, C.T., Kirchner, V., Blackman, C., Pasche, B., Watabe, K., 2019. Ca2+ and CACNA1H mediate targeted suppression of breast cancer brain metastasis by AM RF EMF. EBioMedicine 44, 194–208. https://doi.org/10.1016/j.ebiom.2019.05.038

8-Pall, M.L., 2013. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. Journal of Cellular and Molecular Medicine 17, 958–965. https://doi.org/10.1111/jcmm.12088

9-Sawada, Y., Hosokawa, H., Matsumura, K., Kobayashi, S., 2008. Activation of transient receptor potential ankyrin 1 by hydrogen peroxide. Eur J Neurosci 27, 1131–1142. https://doi.org/10.1111/j.1460-9568.2008.06093.x

10-Messlinger, K., Lennerz, J.K., Eberhardt, M., Fischer, M.J.M., 2012. CGRP and NO in the Trigeminal System: Mechanisms and Role in Headache Generation. Headache: The Journal of Head and Face Pain 52, 1411–1427. https://doi.org/10.1111/j.1526-4610.2012.02212.x

11-Jiang, L., Ma, D., Grubb, B.D.,Wang, M., 2019. ROS/TRPA1/CGRP signaling mediates cortical spreading depression. J Headache Pain 20. https://doi.org/10.1186/s10194-019-0978-z

12-Benemei, S., De Cesaris, F., Fusi, C., Rossi, E., Lupi, C., Geppetti, P., 2013. TRPA1 and other TRP channels in migraine. J Headache Pain 14, 71. https://doi.org/10.1186/1129-2377-14-71

13-Samanta, A., Hughes, T.E.T., Moiseenkova-Bell, V.Y., 2018. Transient Receptor Potential (TRP) Channels, in: Harris, J.R., Boekema, E.J. (Eds.), Membrane Protein Complexes: Structure and Function, Subcellular Biochemistry. Springer Singapore, Singapore, pp. 141–165. https://doi.org/10.1007/978-981-10-7757-9_6

14-Norões, M.M., Santos, L.G., Gavioli, E.C., de Paula Soares Rachetti, V., Otuki, M.F., de Almeida Cabrini, D., da Silveira Prudente, A., Oliveira, J.R.J.M., de Carvalho Gonçalves, M., Ferreira, J., Preti, D., De Logu, F., Nassini, R., André, E., 2019. Role of TRPA1 receptors in skin inflammation induced by volatile chemical irritants in mice. European Journal of Pharmacology 858, 172460. https://doi.org/10.1016/j.ejphar.2019.172460

15-Yang, H., Li, S., 2016. Transient Receptor Potential Ankyrin 1 (TRPA1) Channel and Neurogenic Inflammation in Pathogenesis of Asthma. Med Sci Monit 22, 2917–2923. https://doi.org/10.12659/MSM.896557

16-Kurhanewicz, N., McIntosh-Kastrinsky, R., Tong, H., Ledbetter, A., Walsh, L., Farraj, A., Hazari, M., 2017. TRPA1 mediates changes in heart rate variability and cardiac mechanical function in mice exposed to acrolein. Toxicology and Applied Pharmacology 324, 51–60. https://doi.org/10.1016/j.taap.2016.10.008

17-Kurhanewicz, N., Ledbetter, A., Farraj, A., Hazari, M., 2018. TRPA1 mediates the cardiac effects of acrolein through parasympathetic dominance but also sympathetic modulation in mice. Toxicology and Applied Pharmacology 347, 104–114. https://doi.org/10.1016/j.taap.2018.03.027

18-Durham, P.L., 2016. Diverse Physiological Roles of Calcitonin Gene-Related Peptide in Migraine Pathology: Modulation of Neuronal-Glial-Immune Cells to Promote Peripheral and Central Sensitization. Curr Pain Headache Rep 20, 48. https://doi.org/10.1007/s11916-016-0578-4

19-Cornelison, L.E., Hawkins, J.L., Durham, P.L., 2016. Elevated levels of calcitonin gene-related peptide in upper spinal cord promotes sensitization of primary trigeminal nociceptive neurons. Neuroscience 339, 491–501. https://doi.org/10.1016/j.neuroscience.2016.10.013

20-Nijs J, Torres-Cueco R, van Wilgen CP, Girbes EL, Struyf F, Roussel N, van Oosterwijck J, Daenen L, Kuppens K, Vanwerweeen L, Hermans L, Beckwee D, Voogt L, Clark J, Moloney N, Meeus M., 2014. Applying Modern Pain Neuroscience in Clinical Practice: Criteria for the Classification of Central Sensitization Pain. Pain physician Sep-Oct 2014;17(5):447-57 . https://pubmed.ncbi.nlm.nih.gov/25247901/ .

21-Mayer, T.G., Neblett, R., Cohen, H., Howard, K.J., Choi, Y.H., Williams, M.J., Perez, Y., Gatchel, R.J., 2012b. The Development and Psychometric Validation of the Central Sensitization Inventory: Validation of the Central Sensitization Inventory. Pain Practice 12, 276–285. https://doi.org/10.1111/j.1533-2500.2011.00493.x

22-Kunkler, P.E., Zhang, L., Johnson, P.L., Oxford, G.S., Hurley, J.H., 2018. Induction of chronic migraine phenotypes in a rat model after environmental irritant exposure: PAIN 159, 540–549. https://doi.org/10.1097/j.pain.0000000000001124