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PERSPECTIVES

Genetics of pain and management of chronic pain by extracorporeal depuration therapies

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Abstract

Pain is a very complex subject in biology. As a vital phenomenon, pain must have arisen very early in evolution, since life, in order to defend itself, had to develop among its first capacities the ability to avoid nociceptive stimuli, and it is closely related to the origin of consciousness.The problem of pain involves profound ethical, philosophical, religious and scientific dilemmas, and from the medical point of view, pain is the main reason or cause for which people seek health care. It is estimated that chronic pain affects, for example, one in three Americans and costs this economy $635 billion each year. The experience of pain is distinguished by large differences among individuals. It is subjective, and patients with similar pathologies or diseases report very different levels of pain. This is observed even in controlled experimental settings where pain is studied. Knowledge of genetic and molecular factors underlies the understanding of pain and the development of more effective therapies for its management, and involves a number of methodologies to determine, in the individual experience of pain, which aspects of the basic biological structure are amenable to intervention or quantification.This article address the issue of pain from the genetic point of view and the possible intervention in chronic pain using Extracorporeal Circulation Devices (ECD).

The Problem of Pain

Pain is a complex subject and relative to the sufferer. Its appearance in complex organisms must have been present since very early in evolution, since it is fundamental as a protection mechanism. Its importance lies as an alarm signal to move away from nociceptive stimuli [1] and is closely linked to the emergence of consciousness [2]. The definition of pain most widely accepted by experts gathered at the International Association for the Study of Pain (IASP) is that pain is: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [3].

The problem of pain involves profound ethical, philosophical, religious and scientific dilemmas, and from the medical point of view pain represents the main driver or cause for which people seek health care. Chronic pain is estimated to affect, for example, one in three Americans and costs this economy $635 billion each year [4,5].

The experience of pain is characterized by large differences between individuals. A very important feature is that it is subjective, and patients with comparable pathologies or diseases report dramatically different degrees of pain. This is repeated even in controlled experimental settings where pain is studied [6].

But what accounts for the great interindividual variability in this experience of pain? It is thought to involve numerous biopsychosocial factors, including genetic factors. Other biopsychosocial factors include gender, age, race/ethnicity, personality, and situational variables such as mood, stress, and transient biological factors [6].

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Genetic Factors related to Pain

Pain is a process that occurs in the perception of external stimuli, internal stimuli, or a mixture of both, through the complex neurological system, with components and molecular elements determined by the genetic code. The pain mechanism is programmed through the language of DNA. Therefore, genetic aspects and their variability are basic to understand the phenomenon of pain and interindividual differences [7].

Nociceptive processes

The pain process involves the signal transduction system and therefore involves the participation of structures such as receptors, cells, nerve pathways, intracellular and neuroendocrine mediators among others; in general terms, these are proteins that interact with each other and with other factors, and proteins are produced based on orders written in DNA.

There are multiple phenotypes of pain. But, in the differences that exist between one individual and another, what part is genetic and what part corresponds to other factors? The methodology for studying the contribution of genetic factors to the experience of pain includes animal models, twin studies, family analyses, and genetic association studies [7]. Twin studies compare pairs of monozygotic and dizygotic twins. In these cases, the aim is to study a phenomenon or trait by considering the environment as equal for the sibling pairs. If the tests show greater concordance between monozygotic twins than between dizygotic twins, this concordance is attributed to the fact that the trait has a greater weight of the genetic part in its expression.

To associate genetic variants with pain perception, types of studies known as Genetic Association Studies are performed. Generally, these studies are case-control studies where genetic polymorphisms are investigated. A genetic polymorphism (poly=many, morpho=shape) refers to variations in genetic information and alludes to the fact that the same DNA segment (be it gene, informative unit, or genetic segment of interest) may present interindividual or population differences, and it is these differences that explain why each individual is unique and unrepeatable.

In the case of the genetic study of pain, patients with pain (cases) are compared with unrelated pairs (controls), analyzing whether a particular type of polymorphism is repeated in one or the other case that allows an association to be made with the pain phenotype presented by the patient [27]. A genetic association study can compare the DNA of people with low pain perception with that of people with high pain perception and thus identify genetic differences that may explain the phenotype presented by each.

Genetic polymorphisms can be of multiple types, and can be associated with pathological behaviors or responses. Among the genetic polymorphisms we have RFLPs, AMLPs and SNPs (Single Nucleotide Polymorphisms) [7].

In the case of SNPs ("snips") or Single Nucleotide Polymorphisms, a relatively simple example could be related to the calculation of allele and genotypic frequencies and their association with a given pain phenotype. Allele frequencies refer to the proportion in which an allele or genetic variant is found in a population, while genotypic frequencies refer to the proportion in which two specific alleles combine in the individuals of that population. The combination of two alleles to give rise to a specific genotype is due to the fact that each individual has two alleles or genetic possibilities per gene, corresponding to the contribution of each of its parents. In the case of pain, for example, we could have an allele or genetic variant associated with low pain perception and an allele or genetic variant associated with high pain perception.

Thus, if 60% of the people in a population have the A allele and 40% have the G allele at a given SNP, then the allele frequency of A is 0.6 and the allele frequency of G is 0.4. On the other hand, genotypic frequency is the proportion of a specific combination of alleles in a population. For example, for a given SNP in a specific population, some people would have two copies of the A allele (AA), some people would have one copy of each allele (AG), and others would have two copies of the G allele (GG). These are called genotypes. The genotypic frequency is calculated by dividing the number of people with a given genotype by the total number of people in the population. For example, if 36% of people have the AA genotype, 48% have the AG genotype and 16% have the GG genotype at a given SNP, then the genotypic frequency of AA is 0.36, the genotypic frequency of AG is 0.48 and the genotypic frequency of GG is 0.16. That would mean that in that population 36% of people have a tendency to

have a low pain perception, 48% have an intermediate pain perception and 16% have a tendency to have a high pain perception, i.e. a very low pain threshold and are very sensitive to pain-producing stimuli.

To test this association statistically, researchers use different methods. For example, a common method for testing allele frequencies is called the chi-square test, which compares the observed frequencies with the expected frequencies without association. Another common method for testing genotypic frequencies is called logistic regression, which models the probability of having the disease or trait as a function of genotype and other factors.

This becomes even more complex, when we take into account that there may be multiple SNPs for example (more than two), associated with the pain phenotype, corresponding to minimal gradations in pain perception, as well as many other types of polymorphisms and inter-individual variants, and therefore powerful tools derived from Statistics and Bioinformatics are needed to clarify the data and associations.

Nowadays, there are multiple genes associated with pain and their role corresponds to diverse mechanisms of action, involving ion channels (SCN9A, KCNS1, CACNA2D3, CACNG2), neurotransmitters (GCH1, SLC6A4, ADRB2, HTR2A), and participate in pain facilitation/amplification (KCNS1, SCN9A, ADRB2, H2TRA, CACNG2, IL16), pain protection/decrease (COMT, OPRM1, TRPV1, MC1R, GCH1, CACNA2D3) and modulation of analgesic efficacy (COMT, MC1R, OPRM1, CYP2D6, ABCB1) [8]. There are also some genetic syndromes with congenital insensitivity to pain (see Table 1).

It is very likely that the phenotype resulting from pain, in the part of it corresponding to genetic factors, is the result of effects produced by the interaction of genes in the so-called gene interaction networks and that it is the result of summative effects of amplification and inhibition, caused by specific gene doses, which may be possible to quantify in the future and make predictions in relation to them, establishing quantifiable scales, based on population studies.The role of Epigenetics in pain has also been invoked, that is, the role of environmental factors that can modify gene expression without producing changes in the DNA sequence, including genes related to the pain phenotype. This would imply that our lifestyle habits, including those generated in our internal microenvironment, such as stress, emotions, thoughts, education, culture, and beliefs (which have neuroendocrine effects) [9], could play a role in the expression of pain-related genes. That is, our interactions and environmental factors can generate individual nuances that may affect gene expression, producing unique experiences of pain perception, which are as unique and unrepeatable as each and every living being is unique and unrepeatable.

Fibromyalgia and Chronic Pain

One of the increasingly studied conditions regarding the influence of genetic factors on its clinical course and management is Fibromyalgia. Fibromyalgia is a chronic functional disease presenting with chronic widespread musculoskeletal pain, as well as a constellation of symptoms including fatigue, difficulty sleeping, cognitive dysfunction, stiffness, anxiety and depression. It has a prevalence of 2 - 4% in the general population, with female predominance. The diagnosis of fibromyalgia requires ruling out other organic diseases. To date, there are no specific laboratory tests for the diagnosis of fibromyalgia [10,11].

More recently it is considered that fibromyalgia may be part of a family of related disorders known as Affective Spectrum Disor-

Table 1. List of some genes frequently associated with pain of monogenic origin [28].

Trastorno	Ligamiento	Gen	Proteína
CIDP	2q24	SCN9A	Canal de Sodio Nav 1.7
HSAN tipo I	9q22	SPTLC1	Serina Palmitoil transferasa
HSAN tipo II	12p13	HSN2	Desconocido
HSAN tipo III	9p31	IKBKAP	Proteína Asociada al Complejo IKK
HSAN tipo IV	1q21	NTRK1	Receptor neurotrófico de Tirosina kinasa
HSAN tipo V	1p13	NGFB	Factor de crecimiento neuronal beta

ders (ASD). These include disorders such as Irritable Bowel Syndrome, Chronic Fatigue Syndrome and Migraine, among others [12].

Familial aggregation has been observed in fibromyalgia. The pattern of inheritance is unknown, but it is probably multifactorial. There is evidence that genetic polymorphisms of serotonergic, dopaminergic and catecholaminergic systems play a role in fibromyalgia.

In multifactorial genetic conditions, apart from environmental influence, several genes are considered to be involved. They involve the so-called major genes and minor genes, with a variable relative weight as their name indicates, and mutations in any of them are involved in the susceptibility to suffer from it or may lead to the condition.

Some potential candidate genes associated with fibromyalgia are SLC64A4, TRPV2, MYT1L and NRXN3. In addition, a gene-environment interaction has been proposed as a triggering mechanism, through epigenetic alterations: in particular, fibromyalgia seems to be characterized by a pattern of hypomethylated DNA, in genes involved in stress response, DNA repair, autonomic system response and subcortical neuronal abnormalities [13].

Other genes related to Fibromyalgia include:

- The COMT (Catechol-O-Methyltransferase) gene: it is an enzyme that metabolizes catecholamines (dopamine, norepinephrine), two neurotransmitters active in pain processing. In the val158met polymorphism the amino acid methionine replaces valine producing an enzyme with reduced activity. Homozygotes for met158 show greater pain intensity and higher frequency of negative affective states.

- Gene 5-HTR2A (Serotonin 2A) gene: The T102C polymorphism studied in 168 individuals with FM and 115 controls showed a higher frequency of T/C and C/C genotypes compared to the controls which were predominantly T/T.

- Apo E4: Certain alleles more frequent in post-traumatic FM [14].

In relation to chronic pain, according to the international designation, this is classified as pain lasting more than three months [15]. A popular alternative definition of chronic pain, which does not imply a fixed duration, is "pain that extends beyond the expected period of healing" [16].

Chronic pain varies in different countries and affects between 8% and 55% of the population. It affects women at a higher rate than men, uses a large amount of health care resources worldwide [17], and is a major health problem.

The Classification of Diseases, Eleventh Revision (ICD-11) suggests seven categories for chronic pain [18]:

1. Chronic primary pain: defined by 3 months of persistent pain in one or more regions of the body that is not explained by another pain condition.

2. Chronic cancer pain: defined as visceral (within internal organs), musculoskeletal or bone pain related to cancer or treatment.

3. Chronic post-traumatic pain: pain lasting 3 months after an injury or surgery, excluding infectious or pre-existing conditions.

4. Chronic neuropathic pain: pain caused by damage to the somatosensory nervous system.

5. Chronic headache and orofacial pain: pain that originates in the head or face and occurs 50% or more of the days in a 3 month period.

6. Chronic visceral pain: pain originating in an internal organ.

7. Chronic musculoskeletal pain: pain that originates in the bones, muscles, joints or connective tissue.

Chronic pain can be divided into "nociceptive" (caused by inflamed or damaged tissue that activates specialized pain sensors called nociceptors) and "neuropathic" (caused by damage or malfunction of the nervous system) [19].

Chronic pain is maintained in part by central sensitization, a phenomenon of synaptic plasticity and increased neuronal responsiveness in central pain pathways following painful insults. Accumulating evidence suggests that central sensitization is also driven by neuroinflammation in the peripheral and central ner-

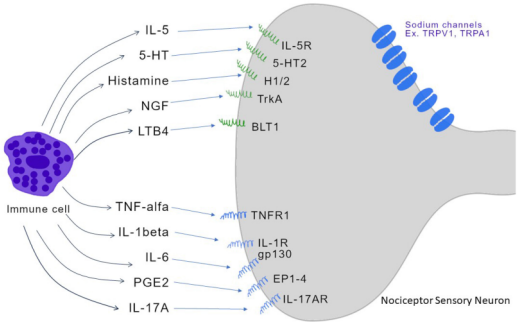
vous system (CNS). A characteristic feature of neuro-inflammation is the activation of glial cells, such as microglia and astrocytes, in the spinal cord and brain, leading to the release of proinflammatory cytokines and chemokines. Recent studies suggest that central cytokines and chemokines are potent neuromodulators and play a sufficient role in the induction of hyperalgesia and allodynia after CNS administration. Sustained increases in cytokines and chemokines in the CNS also promote widespread chronic pain affecting multiple sites in the body. Thus, neuroinflammation drives chronic widespread pain through central sensitization [20]. This whole process is intimately linked to the characteristics of the molecular structure of the components of the pain transmission pathways, and therefore understanding the genetic factors in chronic pain is essential. In Figure 1 you can see some of the proinflammatory factors and their receptors that are part of the nociceptors.

The management of chronic pain, which involves knowledge of the pathophysiology, includes trying to decrease the action of proinflammatory cytokines and tissue chemokines, seeking their inhibition or reduction by various mechanisms. There must be poorly studied genetic differences that make some individuals more susceptible than others in establishing neuroinflammatory patterns. This management is multidisciplinary, but has not achieved completely satisfactory results to date [20]. For example, Interleukin inhibitors such as methotrexate are cytotoxic [21] and/or have an undesirable immunosuppressive effect [22].

New technologies for pain management

Extracorporeal devices are artificial organs that remain outside the body while treating a patient [23]. Extracorporeal depuration therapies (ETD) are treatments increasingly used in intensive care medicine (ICM) departments. Approximately 4% of patients admitted to ICUs require ESRD, with the main indication being acute renal dysfunction (ARD) [24]. Extracorporeal devices are of different types, such as those used in hemodialysis, hemoperfusion, ECMO, ECCO2, liver dialysis devices, extracorporeal ventricular assist device and plasmapheresis/filtration with a variety of indications and applications in each case.

Figure 1. Pro-inflammatory mediator and their receptos in the nociceptor Sensory neuron.



Original concept taken from: Pinho-Ribeiro FA, et. al, Nociceptor Sensory Neuron-Immune Interactions in Pain and Inflammation, 2016, Oct 25, DOI: https://doi.org/10.1016/j.it.2016.10.001

Extracorporeal Blood Purification Devices (EBPD) are able to remove different types of proinflammatory agents by adsorption. In fact, since the COVID-19 pandemic health crisis, authorization was granted for their use for the purpose of removing cytokines associated with SARS-CoV-2 infections [25].

The capabilities of these devices (CytoSorb® adsorbers) include the removal of proinflammatory agents such as IL-1Beta, IL-6, IL-8, IL-10 and Tumor Necrosis Factor (TNF) [26], however, to date, use as an option for chronic pain management is not considered within the possible applications in use.

These extracorporeal blood purification devices (EBPD-Extracorporeal Blood Purification Devices) promise to be excellent effective methods of chronic pain management, as it is considered as a logically feasible option, given the commented pathophysiology of chronic pain [20]. We have observed as an anecdotal experience in our medical practice the case of a patient with chronic pain who came for genetic evaluation of a connective tissue disorder, and in whom a remarkably substantial, but temporary, improvement and relief of her chronic pain condition was observed, as an unexpected therapeutic effect of being treated with this type of devices, as part of the management of a SARS-CoV-2 infection in an Intensive Care Unit (ICU).

In view of these new technologies, it is important to evaluate and protocolize their use to determine the usefulness of these EBPDs as a therapeutic option for the management of chronic pain. New technologies that include more versatile prototypes of smaller dimensions and complexity, depending on the clinical contexts where they will be implemented, should also be taken into account. If feasible and practical, these devices could be used as tools for the management of chronic pain, performing periodic depuration of proinflammatory agents in these patients, so that lower levels of those involved in these processes are maintained, thus causing clinical improvement.

REFERENCIAS

[1] Walters E and Williams A, Evolution of mechanisms and behavior important for pain Phil. Trans. R. Soc. B 2019 3742019027520190275. https://doi.org/10.1098/rstb.2019.0275

[2] Constabile B, The Biological Evolution of Pain. 2023. Socrethics.com

[3] Williams AC, Craig KD. 2016 Updating the definition of pain. Pain 157, 2420-2423. https://doi.org/10.1097/j.pain.0000000000000613

[4] Pizzo PA, Clark NM. Alleviating suffering 101-pain relief in the United States. N Engl J Mewds. 2012; 366;197-199. https://doi.org/10.1056/NEJMp1109084

[5] Gereau RW, Sluka KA, Maixner W, Savage SR, Price TJ, Murinson BB, Sullivan MD, Fillingim RB. A pain research agenda for the 21st century. J Pain. 2014; 15:1203-14. https://doi.org/10.1016/j.jpain.2014.09.004

[6] Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain. 2017 Apr;158 Suppl 1(Suppl 1):S11-S18. https://doi.org/10.1097/j.pain.0000000000000775

[7] Fillingim RB, Wallace MR, Herbstman DM, Ribeiro-Dasilva M, Staud R. Genetic contributions to pain: a review of findings in humans. Oral Dis. 2008 Nov;14(8):673-82. https://doi.org/10.1111/j.1601-0825.2008.01458.

[8] James S. Human pain and genetics: some basics. Br J Pain. 2013 Nov;7(4):171-8 https://doi.org/10.1177/2049463713506408

[9] Vaillant GE. The neuroendocrine system and stress, emotions, thoughts and feelings. Mens Sana Monogr. 2011 Jan;9(1):113-28 https://doi.org/10.4103/0973-1229.77430

[10] Cohen-Biton L, Buskila D, Nissanholtz-Gannot R. Review of Fibromyalgia (FM) Syndrome Treatments. Int J Environ Res Public Health. 2022 Sep 24;19(19):12106. https://doi.org/10.3390/ijerph191912106

[11] Ruschak I, Montesó-Curto P, Rosselló L, Aguilar Martín C, Sánchez-Montesó L, Toussaint L. Fibromyalgia Syndrome Pain in Men and Women: A Scoping Review. Healthcare (Basel). 2023 Jan 11;11(2):223. https://doi.org/10.3390/healthcare11020223

[12] Understanding fibromyalgia and its related disorders. Prim Care Companion J Clin Psychiatry. 2008;10(2):133-44. https://doi.org/10.4088/PCC.v10n0208

[13] D'Agnelli S, Arendt-Nielsen L, Gerra MC, Zatorri K, Boggiani L, Baciarello M, Bignami E. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. Mol Pain. 2019 Jan-Dec;15:1744806918819944. https://doi.org/10.1177/1744806918819944

[14] Reeser JC, Payne E, Kitchner T, McCarty CA . Apolipoprotein E4 Genotype Increases the Risk of Being Diagnosed With Posttraumatic Fibromyalgia, PM&R, Volume 3, Issue 3, 2011, Pages 193-197 https://doi.org/10.1016/j.pmrj.2010.12.009

[15] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. "A classification of chronic pain for ICD-11" 2015. Pain. 156(6): 1003-1007 (June 2015). https://doi.org/10.1097/j.pain.0000000000000160

[16] Turk DC, Okifuji A (2001). "Pain terms and taxonomies". In Loeser D, Butler SH, Chapman JJ, Turk DC (eds.). Bonica's Management of Pain (3rd ed.). Lippincott Williams & Wilkins. pp. 18-25. ISBN 978-0683304626.

[17] Andrews P, Steultjens M, Riskowski J (January 2018). "Chronic widespread pain prevalence in the general population: A systematic review". European Journal of Pain. 22 (1): 5-18. doi:10.1002/ejp.1090. PMID 28815801. https://doi.org/10.1002/ejp.1090

[18] Gereau RW, Sluka KA, Maixner W, Savage SR, Price TJ, Murinson BB, Sullivan MD, Fillingim RB. A pain research agenda for the 21st century. J Pain. 2014; 15:1203-14. https://doi.org/10.1016/j.jpain.2014.09.004

[19] Keay KA, Clement CI, Bandler R "The neuroanatomy of cardiac nociceptive pathways". In Horst GJ (ed.) The nervous system and the heart Humana Press 2000, p 304. https://doi.org/10.1007/978-1-59259-713-0_8

[20] Ji R-R, Nackley A, Huh Y, Terrando N, Maixner W, "Neuroinflammation and Central Sensitization in chronic and widespread pain". Anesthesiology, 2018, August: 129(2): 343-366. https://doi.org/10.1097/ALN.0000000000002130

[21] Hamed KM, Dighriri IM, Baomar AF, Alharthy BT, Alenazi FE, Alali GH, Alenazy RH, Alhumaidi NT, Alhulayfi DH, Alotaibi YB, Alhumaidan SS, Alhaddad ZA, Humadi AA, Alzahrani SA, Alobaid RH. Overview of Methotrexate Toxicity: A Comprehensive Literature Review. Cureus. 2022 Sep 23;14(9):e29518 https://doi.org/10.7759/cureus.29518

[22] Ilinskaya AN, Dobrovolskaia MA. Immunosuppressive and anti-inflammatory properties of engineered nanomaterials. Br J Pharmacol. 2014 Sep;171(17):3988-4000. https://doi.org/10.1111/bph.12722

[23] Churchill Livingstone's mini encyclopaedia of nursing. Internet Archive. Edinburgh; New York: Elsevier/Churchill Livingstone. 2005. p. 200. ISBN 978-0-443-07487-5.

[24] Aguirre-Bermeo H, Tomasa T, Navas A, Xirgu J, Catalán-Ibars RM, Morillas J, Cuartero M, Manciño JM, Roglán A, Utilización de las terapias de depuración extracorpórea en los Servicios de Medicina Intensiva de Cataluña (España), Medicina Intensiva, Volume 39, Issue 5, 2015, Pages 272-278 https://doi.org/10.1016/j.medin.2014.07.001

[25] Shekar K, McAuley DF, Brodie D. Cytokine adsorption during ECMO for COVID-19-related ARDS. Lancet Respir Med. 2021 jul;9(7):680-682. https://doi.org/10.1016/S2213-2600(21)00207-1

[26] Datzmann T, Träger K. Extracorporeal membrane oxygenation and cytokine adsorption. J Thorac Dis. 2018 Mar;10(Suppl 5):S653-S660. https://doi.org/10.21037/jtd.2017.10.128.

[27] Sagoo GS, Little J, Higgins JP. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. PLoS Med. 2009 Mar 3;6(3):e28. doi: 10.1371/journal.pmed.1000028. PMID: 19260758; PMCID: PMC2650724.

[28] James S. Human pain and genetics: some basics. Br J Pain. 2013 Nov;7(4):171-8. doi: 10.1177/2049463713506408. PMID: 26516521; PMCID: PMC4590159.