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Animal models of pain in the study of fibromyalgia

Modelos animales de dolor para el estudio de la fibromialgia

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Keywords:
fibromyalgia, animal models, pain, stress, anxiety, depression.

Palabras clave:
fibromialgia, modelos animales, dolor, estrés, ansiedad, depresión.

Abstract

Fibromyalgia (FM) is a chronic and diffuse type of musculoskeletal pain of non-articular origin. It is characterized by the combination of several symptoms, mainly by the subjective presence of generalized pain, fatigue, morning stiffness and sleep disturbance. The etiology of the disease is multifactorial and nowadays continues to be the subject of study by many research groups. On the other hand, due the complexity of the disease, the implementation of animal models has been proposed, however, choosing the appropriate animal model that meets the characteristics of the symptoms of the disease has generated discrepancies among researchers. For this reason, the objective of this review is to analyze the animal models of pain for the study of fibromyalgia. Search strategies were developed for each database consulted: PubMed, the Web of Science and Embase. The search strategy was carried out using the keywords «fibromyalgia, pain, animal models of pain, generalized pain, chronic pain, neuropathic pain». Pain models were analyzed. The models that are mainly based on pain, whether chronic or neuropathic, are the ones that possess more similarities to the pathology, however, it is not possible to evaluate the emotional component of it, and it is such an important part of the symptoms of fibromyalgia. The complexity of the symptomatology of the disease generates limitations in animal models of pain. The development of experimental designs with animal models of pain for the study of fibromyalgia must consider the limitations analyzed in this review.

Resumen

La fibromialgia (FM) es un tipo de dolor musculoesquelético crónico y difuso de origen no articular. Se caracteriza por la combinación de varios síntomas, principalmente por la presencia subjetiva de dolor generalizado, fatiga, rigidez matinal y alteración del sueño. La etiología de la enfermedad es multifactorial y en la actualidad continúa siendo objeto de estudio por parte de numerosos grupos de investigación. Por otro lado, debido a la complejidad de la enfermedad se ha planteado la implementación de modelos animales, sin embargo, elegir el modelo animal adecuado que cumpla con las características de los síntomas de la enfermedad ha generado discrepancias entre los investigadores. Por ello, el objetivo de esta revisión es analizar los modelos animales de dolor para el estudio de la fibromialgia. Se desarrollaron estrategias de búsqueda para cada base de datos consultada: PubMed, Web of Science y Embase. La estrategia de búsqueda se realizó con las palabras clave «fibromialgia, dolor, modelos animales de dolor, dolor generalizado, dolor crónico, dolor neuropático». Los modelos que se basan principalmente en el dolor, ya sea crónico o neuropático, son los que poseen más similitudes con la patología, sin embargo, no es posible evaluar el componente emocional de la misma, la cual es parte importante de los síntomas de la fibromialgia. La complejidad de la sintomatología de la enfermedad genera limitaciones en modelos animales de dolor. El desarrollo de diseños experimentales con modelos animales de dolor para el estudio de la fibromialgia debe considerar las limitaciones analizadas en esta revisión.

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INTRODUCTION

Fibromyalgia (FM) affects 5% of the population over 18 years. Its prevalence is 2-6% in general medical consultation, in the rheumatology consultation according to different authors it is 3.7-20% with an incidence of 3.9% in women between 20-40 years and 5.8% between 40-60 years.[1] The name of fibromyalgia derives from: «FIBERS» = soft tissues of the body, «MIOS» = muscles and «ALGIA» = pain, thus, «musculoskeletal pain». To this definition, we can add, «chronically generalized and of unknown cause». Years ago, this process was recognized by the name of fibrositis, however, it has not been shown that there is peripheral inflammation, which is why the current name of fibromyalgia has been adopted.[2]

A large proportion of patients present other pathologies associated to FM, such as irritable bowel syndrome, predominantly posterior tension headaches, Raynaud's phenomenon, paresthesia in the upper limbs, and sensation of swelling or swelling in the hands as FM evolves.[2]

Many animal models have been proposed for the study of fibromyalgia. However, these have focused only on some of the symptoms presented in this pathology, without considering the symptoms in general, which is a very complex task since it ranges from emotional manifestations to physical discomfort that causes pain generalized not focused. Hence the main objective of this review is to analyze the animal models of pain, and to point their strengths and weaknesses in relation to the study of this pathology.

SEARCH AND SELECTION STRATEGY OF STUDIES

Search strategies were developed for each database consulted: PubMed, the Web of Science and Embase. The search strategy was carried out using the indexing of MeSH (Medical Subject Headings) terms, combined with Boolean logical operators. In the first search, the keywords «fibromyalgia, animal models, pain». Only original articles written in English and Spanish were included to analyze the animal models of fibromyalgia. A manual inspection of the reference lists of all articles was carried out to ensure the inclusion of important citations. The systematic and comprehensive search of the literature was carried out independently by two researchers that evaluated each abstract and full article, when discrepancies occurred, both researchers reached a consensus. The inclusion criteria were the following: a) original articles that analyzed fibromyalgia related to pain in animal models, b) original articles that analyzed fibromyalgia related to neuropathic pain in animal models, c) original articles that analyzed fibromyalgia related to chronic pain in animal models.

ETHICAL CONSIDERATIONS FOR THE USE OF ANIMAL MODELS

It is vitally important to know the ethical considerations for the proper use and care of laboratory animals that is why during the development of all research involving animals, the biological, environmental, health and ethological conditions must be met required to develop, live healthy and express their normal behavior as a laboratory animal. Likewise, international guidelines for the study of pain with animal models should be considered, such as: ethical standards for investigation of experimental pain in animals; animal pain scales in public policy; ethical decision making about animal experiments.[3] In addition to consulting the Guide for the Care and Use of Experimental Animals.[4]

DESCRIPTION OF THE ANIMAL MODELS OF PAIN

Among the animal models that have been proposed for the study of fibromyalgia, the pain models stand out because they involve the most relevant symptoms of the disease.

In scientific research regarding pain, animal models have obvious advantages over humans regarding to control of genetic factors, environmental factors, safety, management, economics, etc. At the central nervous system level, animal models offer precise neurochemistry and neuroanatomy, as well as excellent temporal and spatial resolution and direct recording of electrophysiology.[5] There are models that due to their nature cannot be carried out in humans for example, it is partial denervation, peripheral nerve ligation,[6] ligation of a part of a large peripheral nerve,[7] or ligation of a complete spinal segmental nerve[8] are common techniques to simulate a mixture of intact and damaged fibers.

Research on pain in fibromyalgia is essential for if new clinically relevant aspects of the mechanisms of nociception or new pharmacological treatments are to be known. Nowadays, many investigations have been generated with different objectives related to pain in animal models, in which painful stimuli (thermal, chemical, mechanical) have been applied with instruments, equipment or validated and standardized

tests (withdrawal of the tail, «tail flick», «hot plate», formalin, carrageenan, etc.).

The pain models most used in animal research are divided depending on the nature of the stimulus, there are four types of painful stimuli, which are: electrical, thermal, chemical, and mechanical. These stimuli can be generated by different methods or techniques. What results in different tests; electric shock in the tail area; hot plate and tail flick are part of the tests with thermal stimulus; formalin and carrageenan are produced by chemical stimuli; foot or tail pressure model generates a mechanical stimulus to the foot or tail.

Experimental studies in conscious animals are called «behavioral studies» which means that all responses, however minimal they may be, are of importance and are part of an animal's behavioral repertoire. The behavioral tests used to study nociception constitute «entry-exit» systems.[9] As a result, when describing these tests, the characteristics of the input (the applied stimulus) and the output (the animal's reaction) must be specified. In animal models, the use of appropriate stimuli to provoke the painful sensation must be quantifiable and reproducible.[10,11]

Electrical stimulation

Electrical stimuli can be generated by subcutaneous electrodes in the rat or mouse tail.[12] When the electrical stimulus is applied a series of behaviors appear successively; a reflex tail movement, vocalization at the time of stimulation, and then vocalization that continues beyond the period of stimulation («post-shock vocalization»). These responses are organized hierarchically; they depend on the different levels of integration of the nociceptive signal in the central nervous system: the spinal cord, the brainstem, and the thalamus.

The application of electrical stimuli has the advantage of being quantifiable, reproducible, non-invasive and of producing synchronized afferent signals. However, it also has serious disadvantages: first, electrical stimuli are not a kind of natural stimuli like those encountered by an animal in its normal environment. More importantly, strong electrical stimuli non-differentially excite all peripheral fibers, including large diameter fibers, which are not directly involved in nociception, as well as fine fibers A and C, which mediate sensations of cold and heat as well as nociceptive information.[9]

The electrical stimulus directly activates peripheral nociceptors through chemical mediators such as cysteic acid, homocysteic acid, N-acetyl aspartyl glutamate, aspartate and glutamate, the latter being an agonist of all receptors for amino acids and is responsible for rapid nociceptive transmission. These mediators convert the stimulus into action potentials which travel through the A fibers. These fibers conduct short latency pain signals that require rapid responses. Subsequently, the afferent fibers synapse on dynamic range interneurons at the level of laminae V, VI, II and IV of the dorsal horn of the spinal cord, releasing somatostatin and ATP, the axons of the dorsal horn neurons are responsible for sending the stimulus through the ascending path of the spinothalamic fasciculus, which leaves the antero-lateral contra-lateral quadrant that collects nociceptive stimuli towards the ventro-postero-lateral pathway of the thalamus, in this area catecholamines such as serotonin, GABA, glycine participate as neuromodulator these neurons subsequently the stimulus is projected to the cortex where the pain is properly encoded to generate a response. This stimulus depends on the voltage to cause pain or analgesia, in fibromyalgia this pain model could not be adequate due to the temporality of the stimulus *(Figure 1)*.

Thermal stimulus

The «hot plate» is a model that uses thermal stimulation, the painful behavior of this model is the reaction time of the animal; it is placed in a cylindrical space with open ends with a floor formed by a metal plate that is heated with a thermostat or a boiling liquid,[13,14] when it is automated, this model presents a great advantage. However, the animal also shows more behaviors during the test (limb licking, vocalization, urination, jumping, etc.) these are considered supraspinal integrated responses that could be a disadvantage if a single behavior is to be recorded.

The specificity and sensitivity of the test can be increased by measuring the reaction time of the first evoked behavior regardless of whether it is paw licking or jumping,[15] or by lowering the temperature.[16] The behavior is relatively stereotyped in the mouse, but it is more complex in the rat, which sniffs, licks its front legs, licks its back legs, straightens, kicks, starts and stops washing, among other things. These behaviors have been labeled «chaotic defensive movements»[17] Espejo and Mir,[18] identified and described 12 different behaviors, there are so many of these behaviors that sometimes some of them

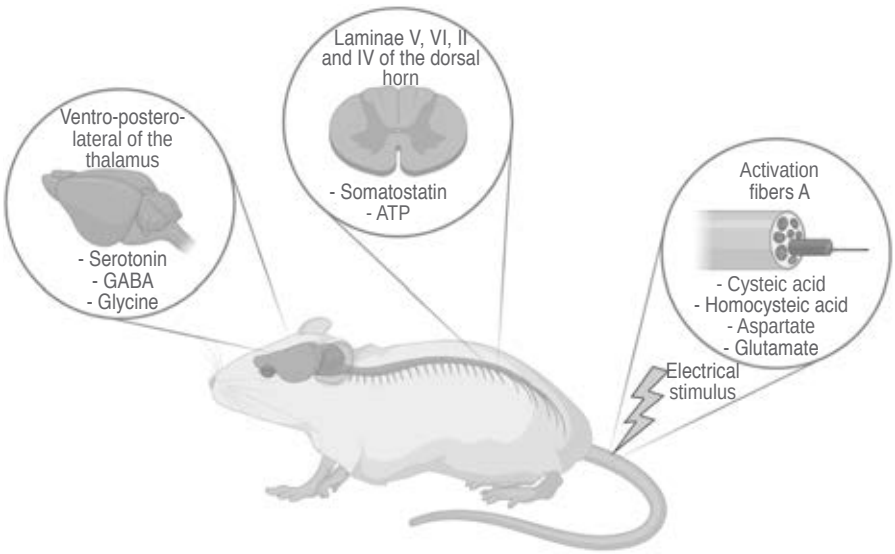

Figure 1: The electrical stimulus directly activates peripheral nociceptors through chemical mediators such as cysteic acid, homocysteic acid, N-acetyl aspartyl glutamate, aspartate and glutamate, the latter being an agonist of all receptors for amino acids and is responsible for rapid nociceptive transmission. These mediators convert the stimulus into action potentials which travel through the A fibers. These fibers conduct short latency pain signals that require rapid responses. Subsequently, the afferent fibers synapse on dynamic range interneurons at the level of laminae V, VI, II and IV of the dorsal horn of the spinal cord, releasing somatostatin and ATP, the axons of the dorsal horn neurons are responsible for sending the stimulus through the ascending path of the spinothalamic fasciculus, which leaves the antero-lateral contra-lateral quadrant that collects nociceptive stimuli towards the ventro-postero-lateral pathway of the thalamus, in this area catecholamines such as serotonin, GABA, glycine participate as neuromodulator these neurons subsequently the stimulus is projected to the cortex where the pain is properly encoded to generate a response. This stimulus depends on the voltage to cause pain or analgesia, in fibromyalgia this pain model could not be adequate due to the temporality of the stimulus.

are difficult to observe. Furthermore, this test is very susceptible to learning phenomena, which result in a progressive shortening of the jump reaction time accompanied by the disappearance of the licking behavior.[17] Therefore, the animal may lick the paws and then jump during the first test, but it will jump almost immediately, certainly with a much shorter reaction time, during the subsequent tests.[19] The «tail flick» is a standardized and widely validated test. This test uses a thermal light beam on the animal's tail that generates a painful sensation. The advantage of this model is that the registration is automated and evaluates the time it takes the animal to withdraw its tail before the stimulus, a disadvantage is the reaction time, because this time is different depending on the area where the stimulus is used. This test is an extremely simplified version of the method used in human subjects by Hardy et al.[20] The application of thermal radiation to an animal's tail causes the tail to be pulled back by a brief and vigorous movement.[21,22] It is the reaction time of this movement that is recorded (often referred to as «tail movement latency»), this is accomplished by starting a timer at the same time as the heat source is applied. An increase in the reaction time is interpreted as an analgesic effect. It is advisable not to prolong the exposure to radiant heat for more than 10 to 20 seconds, otherwise the skin may burn. Thermal stimulation is more selective in the way it stimulates skin receptors. For this reason, specific categories of peripheral axons can be excited, including heat-sensitive and nociceptive fibers. However, the low caloric power has always been a limitation of this method due to the asynchronous activation of peripheral and central neurons.

The thermal stimulus directly activates the polymodal peripheral nociceptors, the stimulus travels through the C fibers, these fibers sense burning pain stimuli and have greater latency. The stimulus reaches the primary afference generating the first synapsis, activating substance P and catecholamines, such as

norepinephrine that acts only on the nociceptors that have been excited, and not on those intact. These fibers synapse on specific medullary interneurons at the level of laminae I, II, IV and V of the dorsal horn of the spinal cord, the axons of the neurons of the dorsal horn are responsible for sending the stimulus through the ascending pathway of the spinal fasciculus thalamic, which leaves the antero-lateral contra-lateral quadrant that collects nociceptive stimuli towards the ventro-postero-lateral path of the thalamus, in this area serotonin participates as a neuromodulator these neurons subsequently project the stimulus to the cortex where it is encoded pain itself to generate a response. In fibromyalgia, a generalized pain can be reported or in a specific place, likewise, a burning pain is reported, due to the signaling route, a thermal pain model could be chosen if one wanted to study an acute temporality of pain in fibromyalgia *(Figure 2)*.

Chemical stimulus

The formalin test is a model of persistent pain, it is divided into two phases; the acute phase and the tonic phase are evaluated by administering 1% formalin in the animal's leg, this administration generates a painful behavior in the animal (shaking of the paw to which the formalin was administered) that is recorded during a period of time, this model is very easy to carry out, however, it is necessary to take into account that the experience of the person who is going to register the painful behavior is crucial for the correct registry. Regarding the carrageenan test, it is an inflammatory pain model that evaluates the degree of inflammation of the limb to which the chemical stimulus was administered, it is a model very easy to apply and to record, it is widely used in many lines of research.[23]

The formalin test is a model of persistent pain. In this test, the first stage reflects acute nociceptive pain

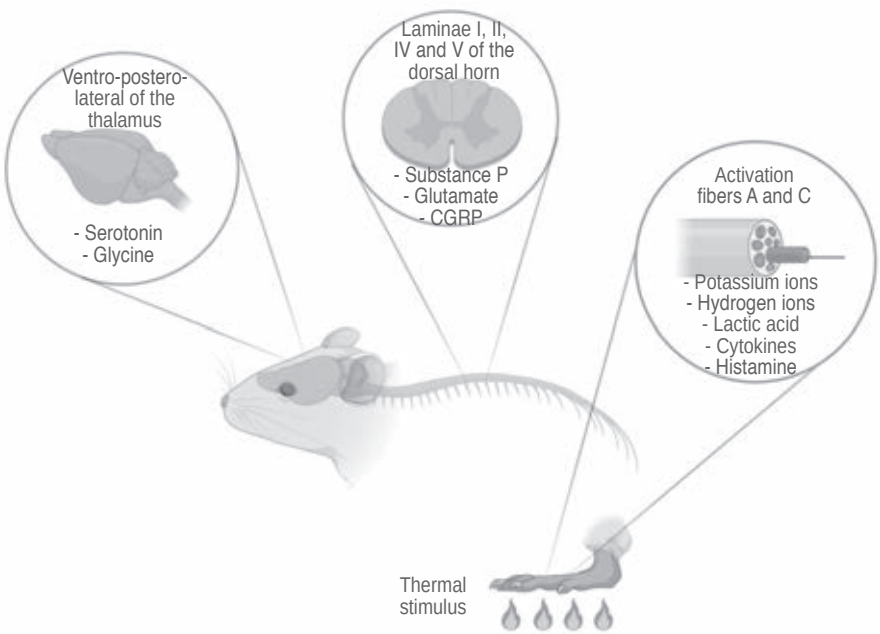

Figure 2: The thermal stimulus directly activates the polymodal peripheral nociceptors, the stimulus travels through the C fibers, these fibers inform about burning pain sensations and have greater latency. The stimulus reaches the primary afference generating the first synapsis, activating substance P and catecholamines, such as norepinephrine that acts only on the nociceptors that have been excited, and not on those intact. These fibers synapse on specific medullary interneurons at the level of laminae I, II, IV and V of the dorsal horn of the spinal cord, the axons of the neurons of the dorsal horn are responsible for sending the stimulus through the ascending pathway of the spinal fasciculus. thalamic, which leaves the antero-lateral contra-lateral quadrant that collects nociceptive stimuli towards the ventro-postero-lateral pathway of the thalamus, in this area serotonin participates as a neuromodulator these neurons subsequently project the stimulus to the cortex where it is encoded pain itself to generate a response. In fibromyalgia, a generalized pain can be reported or in a specific place, likewise, a burning pain is reported, due to the signaling route, a thermal pain model could be chosen if one wanted to study an acute temporality of pain in fibromyalgia.

due to chemical irritation from subcutaneous formalin and the second stage reflects persistent pain. One of its strong points is that it presents a series of signs that can be quantitatively measured and thus, analgesic compounds can be tested in this model. This can be assessed from a postural parameter, protective positions of the affected limb, through active work to alleviate it, such as licking of the affected area or a reflex parameter, such as shaking of the limb. One of the technical drawbacks of this test is that it has an observation period of one hour for each animal and requires great concentration and patience on the part of the researcher. For this reason, attempts have been made to mechanize this task through a computerized assessment by analyzing nociceptive behaviors and motor activity by processing the images recorded by a video camera.[24-26]

The stimulus provided by the subcutaneous injection of formalin is persistent, inducing a behavioral response with a duration of 1 h, unlike tests with mechanical stimuli such as the «tail flick» or «hot plate», the long-lasting stimulus of the formalin test facilitates the observation of feedback modulation and the role of endogenous pain regulation systems, such as opioid and monoaminergic systems.[27]

Carrageenan test is a plantar edema model induced by the administration of carrageenan and is considered as an excellent model of inflammatory pain. A series of complex reactions occurs involving multiple mediators, including histamine, serotonin, metabolites of arachidonic acid via cyclooxygenase, cytokines, neuropeptides. This test can be measured in phases; the non-phagocytic phase begins in the first 60 minutes after carrageenan injection, is characterized by mast cells, cytoplasmic and organelle damage to endothelial cells of blood vessels, as well as expression of interleukin 1 that attracts phagocytes to the site of irritation, an important element in this phase is the increase in substance P. Then the phagocytic phase begins.[28]

Radhakrishnan et al.[29] injected intramuscular carrageenan into unilateral or bilateral triceps of rats, causing muscular hyperalgesia. On the other hand, Sluka et al.[30] provided two intramuscular doses of low pH or pH 4 of acidic saline solution in the gastrocnemius muscle, causing lasting generalized musculoskeletal pain, being these models of the first to treat muscle pain.

Suárez Roca et al.[31] proposed the chronic muscle pain syndrome model. With the forced swimming test (forced swimming test), and carrageenan. But the development of one of the most used models was carried out by Nagakura et al.[32] which consisted of a subcutaneous injection of reserpine dissolved in glacial acetic acid, 1 mL/kg for three consecutive days. By means of electrophysiological tests, they determined several altered parameters. Although this model has been widely used, in 2010, Dr. Gordon Munro made some criticisms of the model proposed by Nagakura and his colleagues in 2009. These criticisms referred to the following aspects: The researcher did not consider the following aspects: pain measurements were only performed in the gastrocnemius muscle and the sole of the right hind leg of the rats, without considering that the discomfort is generalized, in addition, the tests were insufficient to ensure that the animals have fibromyalgia. It should be noted that in the study by Nagakura et al. They only used male rats and the prevalence shows us that it is higher in the female gender, which is why it is criticized that they did not use female rats.[33]

Chemical stimulation involves the administration of agents that cause pain, representing a form of slow, or even very slow, stimulation. In this sense, chemical stimuli are progressive, long lasting, and unavoidable once applied. Its main disadvantages consist in the moment of recording the behavior since it takes personnel with too much experience to discern between the animal's own behavior and a painful behavior.

The chemical stimulus activates peripheral chemoceptors through mediators such as prostaglandins, prostacyclins, leukotrienes, thromboxanes are pain producers and mediators in inflammation, they are substances that enhance secondary pain and sensitize receptors developing hyperalgesia. Likewise, bradycin is present in injured tissues with a great capacity to produce pain. It activates nociceptors through phospholipase C (increases intracellular calcium and depolarizes them), and sensitizes them through phospholipase A2 (through the synthesis of PG E2). This type of stimulus travels through the C fibers with a slow conduction speed of 0.4 to 2 msg. The stimulus reaches the primary afference generating the first synapsis, mediated by calcitonin and the calcitonin gene (CGRP), calcitonin is a polypeptide that is normally found in the brain and its spinal administration produces analgesia. CGRP is involved in pain transmission, is synthesized in spinal ganglia neurons and is released in the posterior horn in areas I, II, and V, increasing the release and effect of substance P and glutamate. In the same

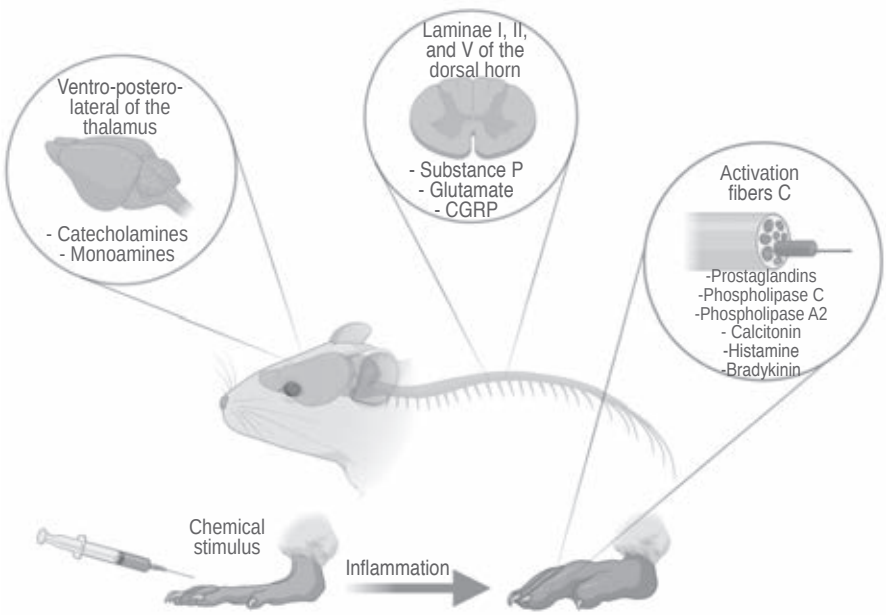

Figure 3: The chemical stimulus activates peripheral chemoceptors through mediators such as prostaglandins, prostacyclins, leukotrienes, thromboxanes are pain producers and mediators in inflammation, they are substances that enhance secondary pain and sensitize receptors developing hyperalgesia. Likewise, bradykinin is present in injured tissues with a great capacity to produce pain. It activates nociceptors through phospholipase C (increases intracellular calcium and depolarizes them) and sensitizes them through phospholipase A2 (through the synthesis of PG E2). This type of stimulus travels through the C fibers with a slow conduction speed of 0.4 to 2 msg. The stimulus reaches the primary afference generating the first synapsis, mediated by calcitonin and the calcitonin gene (CGRP), calcitonin is a polypeptide that is normally found in the brain and its spinal administration produces analgesia. CGRP is involved in pain transmission, is synthesized in spinal ganglia neurons, and is released in the posterior horn in areas I, II, and V, increasing the release and effect of substance P and glutamate. In the same way as electrical and thermal stimuli, the axons of the neurons of the dorsal horn are responsible for sending the stimulus through the ascending path of the spinothalamic fasciculus, which leaves the anterolateral contralateral quadrant that collects nociceptive stimuli. Towards the ventro-postero-lateral pathway of the thalamus, in this area catecholamines and monoamines participate as neuromodulators, these neurons subsequently project the stimulus to the cortex where pain is properly encoded to generate a response. This model could be the most suitable to be used in the study of pain in fibromyalgia, due to the presence of chemical mediators reported in patients with fibromyalgia and the persistence of pain in this model.

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Mechanical stimulus

The most common sites for applying nociceptive mechanical stimuli are the hind leg and the tail. Tests using constant pressure have been progressively abandoned for those applying gradually increasing pressure.[34] In the course of this test, the pressure of increasing intensity is applied to a pinpoint area of the hind leg or, much less frequently, to the tail. In practice, the leg or tail is jammed between a flat surface and a blunt tip mounted on a sprocket system with a slider that can be moved along a graduated beam.[35] These devices allow the application of increasing measurable pressures and the interruption of the test when the

threshold is reached. The measured parameter is the threshold (weight in grams) for the appearance of a certain behavior. When the pressure increases, you can see successively the reflex withdrawal of the paw, a more complex movement by which the animal tries to release its trapped limb, then a kind of struggle, and finally a vocal reaction. The disadvantages of this test are mainly based on (I) how complicated it is to measure the intensity of the stimulus with precision, (II) the repetition of the mechanical stimulus can produce a decrease or on the contrary an increase in the sensitivity of the stimulated part of the body. Body, (III) the need to apply relatively high pressures, which explains the weak sensitivity of the method and (IV) a high variability of the responses.

Finally, the responses produced by noxious mechanical stimuli are classified according to the intensity and/or duration of the stimulus, from reflexes to vocalizations and finally complex motor behaviors. One of the great advantages is that the stimulus stops as soon as a response is obtained, however, it has the disadvantage of activating low-threshold mechanoreceptors as well as nociceptors. Consequently, the stimulus is not specific. There are also technical difficulties in applying mechanical stimuli, especially in freely moving animals. On the other hand, the observed reactions cover a very wide spectrum that goes from the most elementary reflexes to much more compound behaviors (flight, avoidance). In almost all cases, what is monitored is a motor response; vegetative responses are considered only occasionally.[5]

The mechanical stimulus activates peripheral mechanoreceptors that convert this stimulus into action potentials, which travel through the C fibers. These fibers are the largest group and transmit the stimulus with the highest latency. The activation of these nociceptors is through mediators such as prostaglandins, prostacyclins, leukotrienes and thromboxanes. The stimulus reaches the primary afference generating the first synapsis, activating neurotransmitters such as substance P and the calcitonin gene (CGRP) in dynamic range interneurons at the level of laminae V, VI, II, and IV of the dorsal horn of the spinal cord, the axons of the neurons of the dorsal horn are responsible for sending the stimulus through the supraspinal to the ventro-postero-lateral area of the thalamus, this area participates in the transmission of information and analysis of stimuli in relation to the duration, intensity and location. The modulation of pain at the supraspinal level is through serotonin, glycine and other catecholamines, subsequently the stimulus is projected to the cortex where the pain is properly encoded to generate a response. Mechanical stimulation could be used to analyze pain in fibromyalgia due to the chemical measures involved for pain modulation in this model, however, due to the short latency, discrepancies in the results could be generated *(Figure 4)*.

DISCUSSION

Fibromyalgia diagnosis is not that easy, due to the various symptoms it presents, thus, it has been considered a complex and controversial pathology that is triggered by various factors, mainly stress and physical and emotional trauma.[30,36] It occurs mainly in women than in men and its worldwide prevalence is 2 to 3%.[37] Other symptoms such as pronounced fatigue, sleep disorders and psychological disorders (depression and/or anxiety) have been associated.[38] Where depression and anxiety are among the comorbidities that commonly occur in these patients with a prevalence ranging between 20 and 80% and between 13 and 64%, respectively.[39]

Due to the complexity of this pathology and since there is no well-defined etiology, the use and validity of animal models still faces various difficulties, since to generate an animal model of fibromyalgia, chronic pain has been taken as the main symptom, especially if it includes generalized sensitivity. But if we consider that this pathology is triggered or aggravated by multiple physical and/or emotional stressors, such as infections or emotional and physical trauma, the research in models that take only one of the symptoms of this pathology into account, would remain incomplete.[30,36]

However, the models that are mainly based on pain, whether chronic or neuropathic, in many cases they do not consider the emotional aspect as an important part of the symptoms of the disease. Therefore, other models have been developed which address anxiety-depressive aspects employing antidepressant drugs where depression-like behaviors are addressed from the depletion of biogenic amines through the systemic administration of reserpine.[32] But the question arises again, whether more importance should be given to the emotional or the physical component. The most obvious case is from Liu et al.[40] who proposed the model of chronic generalized musculoskeletal pain induced by repeated intramuscular acid injections in rodents, where, according to the authors, the conditions are closer to those in fibromyalgia are

replicated. But the evaluation of the consequences of anxiety and depression is pending. On the other hand, anxiety-depressive models have been generated that are mainly based on stress caused by intermittent cold stimuli or repeated cold stress,[41] the unpredictable sound stress model,[42,43] or sub chronic swimming stress that induces generalized chronic pain.[44] Recently an interesting approach has been to evaluate the IgG of fibromyalgia patients in animal models,[45] this approach could also be applied to other molecules that could be participating in both the nociceptive and the emotional components.

In the present work, the different types of animal models of pain for the study of fibromyalgia have been analyzed. However, we cannot put aside the relationship between pain and emotional/cognitive alterations. Taking stress as one of the main symptoms of fibromyalgia patients, Khasar et al.[41] devised the DCG model, which consists of inducing stress through unpredictable sounds. Furuta et al.[46] devised the FMS model, SVI/CI, with an intramuscular injection of HCl, pH 4 bilaterally in the gluteal muscles and an injection of intravesical polyethylene catheter + saline + 1% lidocaine. Green et al.[41] proposed the model of FMS, SVI, anxiety, and temporomandibular disorder. That caused stress through unpredictable sounds and stress through avoidance of water. In addition to stress, he evaluated nociception, by means of the forced swimming test (forced swimming test), using intramuscular carrageenan to cause pain. These models were used for the study of fibromyalgia, however, the authors report limitations in the models due to the complexity of the symptoms.

Although, as has been presented throughout the text, this direct correlation is not necessarily present, since as mentioned above, some observations suggest

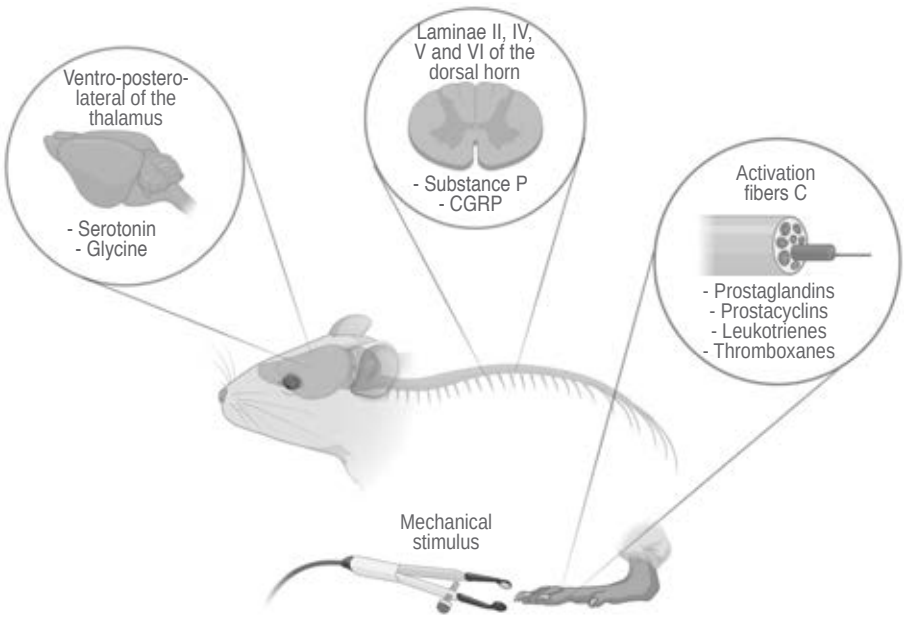

Figure 4: The mechanical stimulus activates peripheral mechanoreceptors that convert this stimulus into action potentials, which travel through the C fibers. These fibers are the largest group and transmit the stimulus with the highest latency. The activation of these nociceptors is through mediators such as: prostaglandins, prostacyclins, leukotrienes and thromboxanes. The stimulus reaches the primary afference generating the first synapsis, activating neurotransmitters such as substance P and the calcitonin gene (CGRP) in dynamic range interneurons at the level of laminae V, VI, II and IV of the dorsal horn of the spinal cord, the axons of the neurons of the dorsal horn are responsible for sending the stimulus through the supraspinal to the ventro-postero-lateral area of the thalamus, this area participates in the transmission of information and analysis of stimuli in relation to the duration, intensity and location. The modulation of pain at the supraspinal level is through serotonin, glycine and other catecholamines, subsequently the stimulus is projected to the cortex where the pain is properly encoded to generate a response. Mechanical stimulation could be used to analyze pain in fibromyalgia due to the chemical measures involved for pain modulation in this model, however, due to the short latency, discrepancies in the results could be generated.

a temporal dissociation and partially independent mechanisms between these aspects of chronic pain and anxiety-depressive disorders, thus, mechanisms that trigger the different symptoms present in fibromyalgia make it a multifactorial process.

It should be noted that not all patients with chronic pain have mood disorders, therefore, for us to understand the interaction and coexistence of pain and mood disorders, it would be essential to develop studies on said resilience/susceptibility in animal models. At the same time, it is necessary to develop alternative tests to behavioral ones, such as neuroimaging or biochemical biomarkers, to better characterize the anxiety-depressive consequences of chronic pain.

In this context, the development of experimental designs that do not take these comorbidities into account in a single model can be taken as a limitation of the studies.

Although there may be some imperfections or limitations of the animal models, they have provided very useful information to understand the mechanisms that are involved in the main symptoms of this pathology. In the future, studies of a transitional nature should be carried out to combine the results obtained in the different models in order to be able to develop pharmacological, psychological, social interaction therapies and what is new in gene therapies.

PERSPECTIVE

Future studies should consider the comorbidities that accompany fibromyalgia, either as added symptoms or as a consequence of the pain that develops during the evolution of this pathology. Patients with pain experience disability, anxiety, depression, cognitive dysfunction, sleep disturbances, loss of libido, social isolation, and any other symptoms that could be generated in animal models. The need for a greater understanding of the fundamental physiology underlying pain will persist as long as the treatment of patients with acute/chronic/neuropathic pain remains relatively ineffective. In the area of scientific research, we do not see any scenario in the short or medium term in which real advances are possible without the participation of animal models. That said, we believe that the combination of human studies together with studies in animal models is increasingly relevant and leads us to a much more specific, homogeneous, and translatable knowledge than has been the case so far. Therefore, we believe that the time has come for true cross-national research on fibromyalgia.

CONCLUSION

Fibromyalgia has not yet been fully explored with the purpose of making an exclusive model of it. The knowledge acquired in this range of models makes us go deeper into the knowledge of this disease that every day increases in the world population, so every effort made to develop adequate treatments brings us closer to a better comprehensive treatment. Despite the lack of more multicenter studies, the progress made leads us to improve the quality of life of patients who suffer from it.

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