Decreased Corneal Sensitivity and Tear Production in Fibromyalgia

Juana Gallar,[1] *Celia Morales,*[2] *Vanesa Freire,*[2] *M. Carmen Acosta,*[1] *Carlos Belmonte,*[1] *and Juan A. Duran*[2,3]

Purpose. To investigate corneal sensitivity to selective mechanical, chemical, heat, and cold stimulation in patients with fibromyalgia (FM).

Methods. Twenty patients with FM (18 women, 2 men; 51.9 ± 2.3 years old) and 18 control subjects (16 women, 2 men; 51.7 ± 2.4 years) participated voluntarily in the study. Subjective symptoms of ocular dryness were explored and a Schirmer I test was performed. The response to selective stimulation of the central cornea with the Belmonte gas esthesiometer was measured.

Results. The majority (18/20) of patients with FM reported dry eye symptoms, with the ocular dryness score significantly higher in affected subjects than in healthy ones (2.3 ± 0.1 vs. 0.05 ± 0.02; $P < 0.001$). The Schirmer test results were significantly lower in patients with FM than in those in the control group (10.5 ± 2.2 and 30.6 ± 1.6 mm, respectively; $P < 0.001$). Mean corneal threshold sensitivity values to chemical stimulation (31.16% ± 2.04% CO_2 FM; 15.72% ± 0.67% CO_2 control), heat (1.87 ± 0.11°C FM; 0.99 ± 0.05°C control), and cold (−2.53 ± 0.11°C FM; −0.76 ± 0.05°C control) were increased in patients with FM, whereas threshold responses to mechanical stimulation did not vary significantly (123.0 ± 8.0 mL/min FM; 107.8 ± 4.4 mL/min control).

Conclusions. The reduced corneal sensitivity of patients with fibromyalgia is attributable to a moderate decrease in corneal polymodal and cold nociceptor sensitivity, which may be the consequence or the cause of the chronic reduction in tear secretion also observed in these patients. (*Invest Ophthalmol Vis Sci.* 2009;50:4129–4134) DOI:10.1167/iovs.08-3083

Fibromyalgia (FM) is a common disorder characterized by chronic, diffuse, widespread pain in combination with tenderness at specific sites on digital palpation. It affects approximately 3% of the population in developed countries.[1,2] There is controversy about socioeconomic, educational, and ethnic distribution of FM, and a female–male ratio of approximately 8:1 has been reported.[1–3] Among many other symptoms and signs, a substantial portion of patients with FM present concomitant symptoms of ocular and oral dryness,[4–6] with ocular discomfort being a common complaint. The ocular surface alteration in FM has been reported to include alteration of tear production, but as is often the case among the general population, most patients with FM with such dry eye symptoms do not satisfy criteria for Sjögren's syndrome (SS)[6] and usually receive diagnoses of dry eye and mouth syndrome (DEMS).[4] Despite abundant data on the general manifestations of FM, little is known about its ocular complications, in particular those concerning corneal sensitivity. The purpose of this study was to measure and correlate tear production and corneal sensitivity to selective mechanical, chemical, and thermal stimulations in patients with FM.

Methods

Patients

Twenty patients of both sexes (18 women, 2 men) who had a diagnosis of FM based on recognized criteria and had been prescribed selective serotonin reuptake inhibitors, tri- or tetracyclic antidepressants, dual serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, NSAIDs, or no pharmacologic treatment were recruited from an association of patients with FM (Asociación de Fibromialgia del País Vasco) and participated voluntarily in the study. Exclusion criteria were a history of ocular infection or chronic inflammation, glaucoma, current use of ocular medication, contact lens wear, and previous intraocular surgery. The subjects signed an informed consent to a protocol approved by the Ethics Committee of the University Miguel Hernández and were free to discontinue the examination at any time. The protocol adhered to the tenets of the Declaration of Helsinki and European Union regulations.

Using the same exclusion criteria, we selected a group of 18 age- and sex-matched volunteers without FM as the control group, thus avoiding differences due to age and sex.[7]

Seventy-six eyes of 38 subjects were examined. Table 1 summarizes the demographic data of the subjects enrolled in this descriptive study as the control and FM groups. Statistical analysis showed no difference in sample size, mean age ($P = 0.868$, *t*-test), and proportion of male and female subjects ($P = 0.676$, *z*-test) between the two groups.

All volunteers completed a questionnaire to quantify ocular discomfort and ocular surface dryness, validated for the diagnosis of dry eye in people who have Spanish as their first language.[8] The questions included were related to ocular symptoms, environmental triggers, and visual impairment.

The ocular surface of each patient was examined with the slit lamp after lissamine green vital staining before sensitivity testing. All corneas were characterized by the absence of clinical signs of keratopathy and of epithelial defects and corneal opacities. After corneal esthesiometry, the Schirmer test was performed.

Corneal Esthesiometry

The Belmonte noncontact gas esthesiometer (an instrument originally designed at the Instituto de Neurociencias de Alicante) was used to explore corneal sensitivity thresholds to selective mechanical, chemi-

From the [1]Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, San Juan de Alicante, Spain; and [2]Instituto Clínico Quirúrgico de Oftalmología and [3]Facultad de Medicina, Universidad del País Vasco, Bilbao, Spain.

Supported by Grants SAF2005-00277, SAF2008-00529, BFU2008-04425, and CSD2007-00023 from the Ministerio de Ciencia e Innovación; Grant GV/2007/030 from the Generalitat Valenciana; and the Fundación Marcelino Botín, Spain.

Submitted for publication October 30, 2008; revised January 19, 2009; accepted June 5, 2009.

Disclosure: **J. Gallar**, None; **C. Morales**, None; **V. Freire**, None; **M.C. Acosta**, None; **C. Belmonte**, None; **J.A. Duran**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Juana Gallar, Instituto de Neurociencias de Alicante, Universidad Miguel Hernandez-CSIC, Avda, Santiago Ramon y Cajal, s/n, 03550 Sant Joan d'Alacant, Spain; juana.gallar@umh.es.

TABLE 1. Demographic Data

	FM	Control
Number	20	18
Age (y)		
Mean	51.9 ± 2.3	51.7 ± 2.4
Range	34–67	33–67
Female/male ratio	18/2	16/2

Data are expressed as the mean ± SEM.

cal, heat, and cold stimuli.[9–11] This instrument applies gas jets to the corneal surface of 3 seconds' duration separated by a 2-minute pause. For selective mechanical stimulation, pulses of air of increasing flow (from 0–300 mL/min) were applied. Selective chemical stimulation was performed with gas pulses containing a mixture of air and CO_2 at increasing concentrations (0%–80% CO_2), applied at a subthreshold flow. To prevent sensations evoked by changes in corneal temperature during mechanical and chemical stimulation, the stimulating gas was heated to 50°C at the tip of the probe, which corresponded to a gas temperature at the surface of the cornea of approximately 34°C.[9]

Selective hot and cold thermal stimulation consisted of pulses of air at different temperatures at the tip of the probe (+5° to +80°C) applied at a flow below mechanical threshold. Those pulses induce corneal surface temperature variation ranging between −3.5°C and +2.5°C around the basal temperature value of 34.5°C.[10]

Experimental Protocol

The subject was seated in front of a slit lamp table with the head supported by a holder. The tip of the esthesiometer probe was placed perpendicular to the center of the cornea, at a distance of 5 mm from the corneal surface. The subject was asked to blink immediately before each pulse and to keep the eye open during the gas jet application. He or she identified the onset and offset of the stimulus with a gentle click produced by the opening and closing of a valve inside the probe. Selective mechanical, chemical, and thermal stimuli were applied to both eyes, always starting with the mechanical sensitivity exploration. Pulses of each modality of stimulus were subsequently applied at random. Subjects ignored the modality of stimulation that was applied.

Immediately after each pulse, the subject was asked to respond verbally whether he or she had felt the stimulus. The mechanical sensitivity threshold was determined by using the method of levels.[12] The sensation threshold for chemical and thermal stimulation was assessed taking as the threshold the lowest stimulus intensity that evoked a positive response.[10,11,13] Subjects were also asked to describe the quality of the sensation evoked by each stimulus in their own words.

After sensitivity was tested in both eyes, the Schirmer I test was performed on the left eyes of all subjects. The protocol was completed in a single session, performed during morning hours by the same investigator. Temperature and humidity of the room were kept constant (~23°C and 55%, respectively).

Statistical Analysis

No significant differences were found in individuals between thresholds in the right and left eyes (paired *t*-test, data not shown). Therefore, data of both eyes from each subject were averaged and taken as a single value. The Mann-Whitney rank sum test and *t*-test were used to assess differences between the control and FM subjects. Data were collected and processed for statistical analysis (SigmaStat; SPSS, Chicago, IL). All data are expressed as the mean ± SEM.

RESULTS

Clinical Symptoms

No symptoms of discomfort or dryness were reported by the individuals in the control group, whereas symptoms of ocular discomfort and dryness with different levels of severity were present in 18 of 20 of the patients with FM, the difference between the results obtained from both groups being significant (Table 2). Also, the FM group showed significantly lower Schirmer I test results in comparison with the control group (Table 2; Fig. 1A). No significant differences in Schirmer's test result associated with age were found within the FM or control group (correlation coefficients: −0.064 and −0.307; $P = 0.790$ and 0.214, respectively; Fig. 1B).

Corneal Esthesiometry

The mechanical threshold response to air pulses of neutral temperature applied to the center of the cornea in the 20 patients with FM varied between 75 and 200 mL/min, slightly higher than those observed in the control subjects, but the differences were not significant (average threshold flow: 122.95 ± 8.00 mL/min vs. 107.75 ± 4.35 mL/min; $P = 0.279$, Mann-Whitney rank sum test; Table 3, Fig. 2A).

Mechanical stimulus was described by both groups of patients as a mild irritating sensation, usually with a stinging component. No correlation was found between mechanical threshold and age in the patients with FM ($P < 0.379$, Pearson correlation; Fig. 3A), whereas in the control subjects, mechanical threshold increased proportionally with age ($P < 0.001$, Pearson correlation; Fig. 3A).

The mean threshold for selective chemical stimulation was significantly higher in the patients with FM than in the control group ($P < 0.001$, Mann-Whitney test; Table 3, Fig. 2B). Chemical thresholds did not tend to increase with age in the subjects with FM ($P = 0.378$, Pearson correlation; Fig. 3B), contrary to the responses of the control subjects ($P = 0.045$, Pearson correlation; Fig. 3B). The sensation evoked by CO_2 was defined by all subjects as irritating, with stinging, burning, and pricking components. A significantly lower sensitivity was obtained with heat stimulation, with a threshold value significantly higher than that control in the patients with FM ($P < 0.001$, Mann-Whitney test; Table 3, Fig. 2C), with no correlation between threshold and age ($P = 0.851$, Pearson correlation; Fig. 3C) contrary to the responses of the control subjects, in whom threshold and age correlated positively ($P = 0.002$, Pearson correlation).

Likewise, an elevated threshold value to cold stimulation was observed in the patients with FM in comparison with the control individuals ($P < 0.001$, Mann-Whitney test; Table 3, Fig. 2D). Cold threshold responses did not correlate with age in the patients with FM ($P = 0.637$, Pearson correlation; Fig. 3D), whereas in the control subjects the correlation was significant ($P < 0.001$; Fig. 3D).

Spearman correlation analysis showed no association between the medication received by the patients with FM and the

TABLE 2. Ocular Symptoms and Tests

	FM	Control
Discomfort and ocular dryness questionnaire* (0 to 4)	2.27 ± 0.13† (0–4, 3)	0.05 ± 0.02 (0–2, 0)
Schirmer test (mm)	10.5 ± 2.2† (range 1–27, 5.5)	30.6 ± 1.6 (20–40, 31.3)

Data are expressed as the mean ± SEM; $n = 20$ and 18 for FM and control, respectively. Data in parentheses are the range and median.

* Single score for symptoms: 0, never; 1, seldom; 2, sometimes, no discomfort; 3, frequent, with discomfort; 4, frequent, with discomfort and interference with activity.

† $P < 0.001$, Mann-Whitney rank sum test.

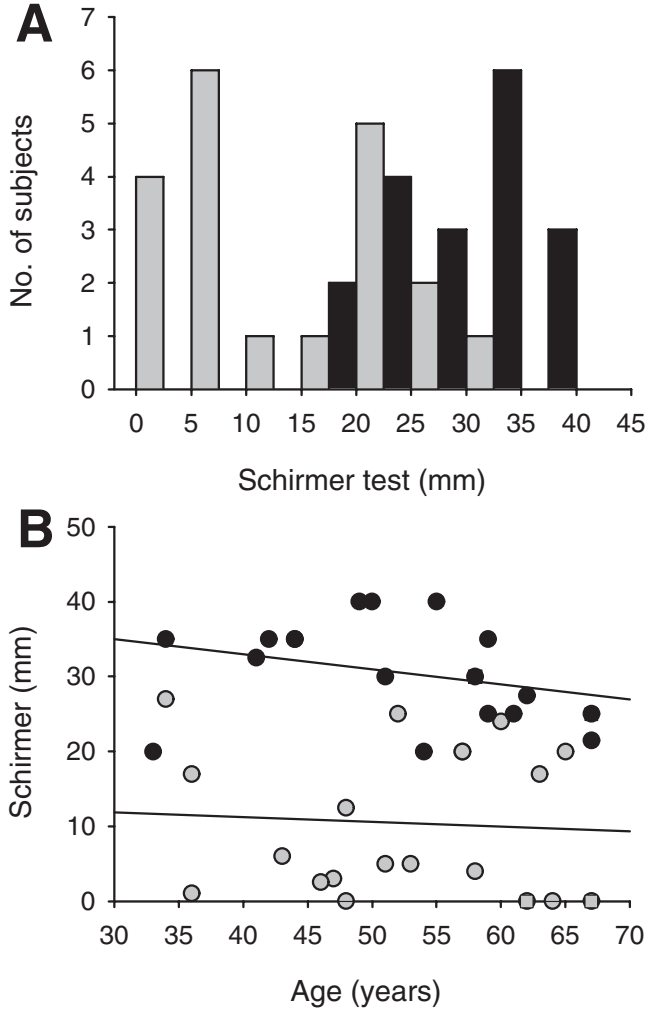

FIGURE 1. Schirmer test results in control subjects and patients with FM. (**A**) Frequency distribution of the Schirmer test results (length of thread wetness, in millimeters) showing the difference between control subjects (*black columns*) and FM patients (*gray columns*). $P < 0.001$; Mann-Whitney. (**B**) Distribution of Schirmer test data with age, in control (*black symbols*) and FM (*gray symbols*) subjects for males (*squares*) and females (*circles*). Linear regression analysis did not show significant differences with age in the FM or control group.

threshold responses to mechanical, chemical, heat, and cold (data not shown).

DISCUSSION

Our results show a reduced tear secretion and a significantly higher threshold for conscious detection of noxious chemical and thermal stimuli applied to the cornea in patients with FM, in comparison with control subjects. Within the FM group, the patients showed the same profile of sensitivity deficiency irrespective of their age, suggesting that sensory deterioration appears early in the development of FM and is independent of age.

A relation between chronic fatigue and Sjögren's syndromes has been reported.[4–6] Confirming these results, in the present work a significant decrease in tear secretion in the patients with FM compared with the controls was recorded, although reductions in tear secretion measured in patients with FM were not as pronounced as those in patients with dry eye of other etiologies.[14,15] Some of the patients participating in the study were taking medications that can potentially modify tear secretion, such as antidepressants.[16] However, no correlation was found between the observed changes in tear secretion and the medications administered to the patients.

In this work, patients with FM exhibited significantly higher corneal sensibility thresholds to CO_2, heat, and cold than did normal subjects, whereas the mechanical threshold was not significantly altered. It has been postulated that with the Belmonte gas esthesiometer, when air at increasing flow rates is applied at the temperature of the corneal surface of 34°C (mechanical stimulation), the corneal Aδ and C polymodal nociceptors are predominantly activated accompanied by recruitment of the Aδ mechanoreceptors.[10] With gas mixtures of increasing CO_2 concentration, a proportional decrease in pH occurs at the corneal surface.[17] This decrease acts as a specific stimulus for polymodal nociceptors of the cornea, of an intensity proportional to the local pH reduction. Likewise, hot air applied to the cornea selectively activates polymodal nociceptors, simultaneously silencing the spontaneously active cold receptors. Finally, moderate cooling exclusively stimulates cold receptors, whereas polymodal nociceptors appear to be weakly recruited by cold air only when corneal temperatures below 29°C are attained.[10] Thus, our observation of higher corneal sensitivity thresholds in the patients with FM suggests that sensory pathways activated by a selective stimulation of the various functional types of corneal sensory receptors are disturbed to a variable degree, with pathways activated by polymodal and cold corneal receptors more markedly affected.

In studies performed in normal and FM-affected subjects, where heat and cold stimuli were applied to the arm's skin with a contact thermal stimulator, sensory thresholds for innocuous warm and cold stimuli were normal in patients with FM, whereas pain was evoked with heat and cold stimuli of significantly lower intensity.[18] However, in these patients, the subjective pain threshold as well as the threshold of the nociceptive flexion reflex evoked by electrical stimulation of the sural nerve (a procedure that short circuits peripheral transduction mechanisms) were also lower than normal, suggesting that the main disturbance in patients with FM is an abnormal processing of the sensory input at central nociceptive pathways.[18] Also, pain evoked by repeated thermal stimuli (temporal summation of second pain, TSSP) was abnormal in FM subjects. TSSP is considered to reflect central sensitization by C-nociceptor input of dorsal horn neurons and is dependent on stimulus frequency,[19] further suggesting that an alteration of central pain sensitivity rather than peripheral sensitization is behind the en-

TABLE 3. Sensation Threshold Responses to Selective Stimulation of the Cornea

Stimulus	FM	Control
Mechanical (air flow, mL/min)	122.95 ± 8.00 (75 to 200)	107.75 ± 4.35 (65 to 137.5)
Chemical (CO_2 in air, %)	31.16 ± 2.04* (18.75 to 50)	15.72 ± 0.67 (12 to 20.5)
Heat (temperature change, °C)	+1.87 ± 0.11* (0.9 to 2.9)	+0.99 ± 0.05 (0.26 to 1.18)
Cold (temperature change, °C)	−2.53 ± 0.11* (−1.9 to −3.5)	−0.76 ± 0.05 (−0.38 to −0.94)

Data are the mean ± SEM (range); $n = 20$ and 18 for FM and control, respectively.

* $P < 0.001$, Mann-Whitney rank sum test.

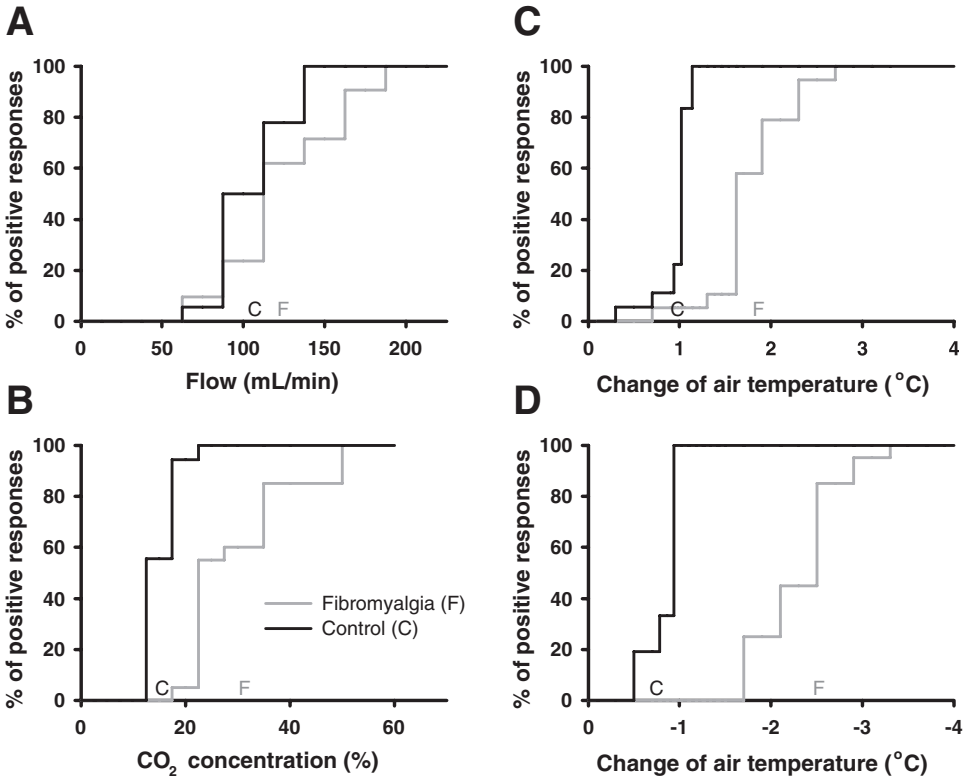

FIGURE 2. Cumulative distribution of threshold responses to (**A**) air pulses of increasing flow (mechanical stimulation), (**B**) pulses with increasing CO_2 concentration (chemical stimulation), (**C**) pulses of air at increasing temperatures (hot thermal stimulation), and (**D**) pulses of air at decreasing temperatures (cold thermal stimulation), in FM (*gray line*) and control (*black line*) patients.

hanced pain in patients with FM. Our observation that sensitivity of the cornea to noxious heat and chemical stimuli is decreased in the patients with FM also supports the interpretation that peripheral nociceptors are not directly sensitized in this disease. On the contrary, in the cornea the excitability of polymodal nociceptor endings appeared to be decreased, whereas mechanoreceptor sensitivity was apparently less affected.

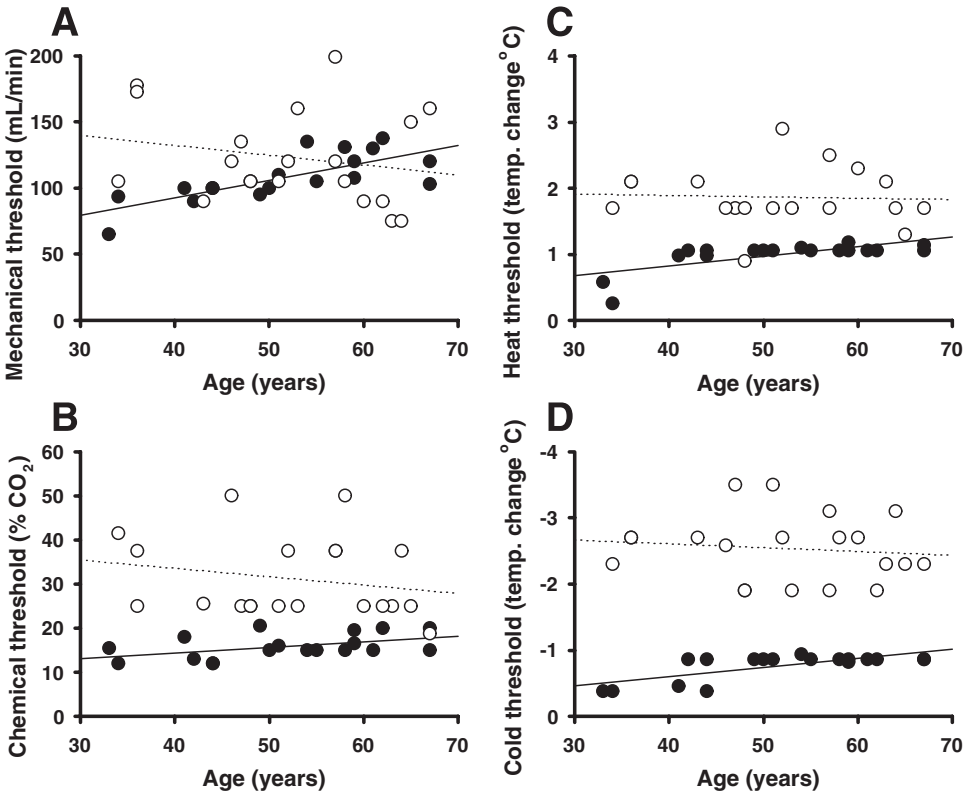

FIGURE 3. Relationship between age and corneal sensitivity threshold responses to mechanical (**A**), chemical (**B**), heat (**C**) and cold (**D**) stimuli in patients with FM (○) and in a group of age and sex-matched control subjects (●). Linear regression curves of the respective data are also plotted.

It has been proposed that tear secretion is controlled by the lacrimal functional unit consisting of the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland and the interconnecting innervation. If any portion of this functional unit is compromised, lacrimal gland support to the ocular surface is impeded.[20,21] Thus, it is possible that a moderate tear dysfunction in patients with FM causes an impairment of polymodal nociceptor activity and a reduction of corneal sensitivity. Alternatively, corneal nerves could be functionally altered in FM and as a consequence of their reduced sensory input, tear secretion driven by tonic nerve activity is decreased, thus causing ocular dryness.

In ocular eye dryness of other etiologies, corneal sensitivity to all stimulus modalities (chemical, thermal, and mechanical) measured with the same model of esthesiometer used in the present experiments, was below normal,[14,15] although hypersensitivity in moderate ocular dryness has also been reported using the modified Belmonte esthesiometer.[22] This sensory impairment was attributed to abnormal responsiveness of sensory nerve endings of the cornea secondary to injury and inflammation of the corneal epithelium accompanying chronic dryness of the ocular surface. Therefore, if a reduced tear secretion is part of the pathologic disturbances present in patients with FM, a parallel decrease of corneal sensitivity would not be surprising.

On the other hand, it has been proposed that changes in background activity of corneal sensory nerves, which are part of the lacrimal functional unit modify tear secretion and may lead to ocular dryness.[21] The reduced corneal sensitivity in patients with FM contrasts with the observation made in other tissues where FM has always been associated with local or generalized tenderness evidenced as widespread mechanical hyperalgesia and allodynia.[23] Changes in nociceptor tonic peripheral input, particularly from muscle nociceptors in patients with FM have been repeatedly suggested.[23] In these patients, palpation of deep tissues reveals an enhanced nociceptive sensitivity that was not restricted to the regions of clinical pain. Similarly, psychophysical testing evidenced the development of allodynia and hyperalgesia to cutaneous stimulation at locations beyond regions of clinical pain referral. Moreover, FM-associated pain can be abolished by removal of pain sensory input from the periphery.[24] In most tissues, an increased sensitivity to direct repeated noxious stimulation has been reported, although pressure pain thresholds exhibited slight differences.[25–27] Thus, our data speak against a widespread sensitization of peripheral nociceptors in all territories that have been suggested as the main cause of central hyperexcitability of the nociceptive system in FM[28] and favor instead the interpretation that an alteration of central pain sensitivity is behind the enhanced pain in patients with FM.[19] Our results further suggest that in patients with FM, central sensitization of the trigeminal sensory pathways supplied by corneal fibers is either absent or counterbalanced by the reduced sensitivity of peripheral corneal nerve fibers.

It appears reasonable to conclude that the reduced responsiveness to corneal stimulation in patients with FM is caused by decreased sensitivity of corneal polymodal nociceptors secondary to an impairment of their transducing capabilities. From our results, it cannot be determined whether this is a direct effect of the disease on peripheral sensory endings, which would be surprising considering the opposite effects in nociceptors of other territories, or is secondary to peripheral nerve ending damage secondary to the ocular surface dryness that develops in patients with FM, as is the case in patients with dry eye of other origins.[14,15]

Acknowledgments

The authors thank Alfonso Pérez-Vegara and Manuel Bayonas for technical assistance.

References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160–172.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58:26–35.
3. Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol.* 1995;22:151–156.
4. Price EJ, Venables PJW. Dry eyes and mouth syndrome: a subgroup of patients with sicca symptoms. *Rheumatology.* 2002;41:416–422.
5. Calabrese LH, Davis ME, Wilke WS. Chronic fatigue syndrome and a disorder resembling Sjögren's syndrome: preliminary report. *Clin Infect Dis.* 1994;18(suppl 1):S28–S31.
6. Bonafede RP, Downey DC, Bennett RM. An association of fibromyalgia with primary Sjögren's syndrome: a prospective study of 72 patients. *J Rheumatol.* 1995;22:133–136.
7. Acosta MC, Alfaro ML, Borrás F, Belmonte C, Gallar J. Influence of age, gender and iris color on mechanical and chemical sensitivity of the cornea and conjunctiva. *Exp Eye Res.* 2006;83:932–938.
8. Donate J, Benitez del Castillo JM, Fernandez C, Garcia-Snachez J. Validation of a questionnaire for the diagnosis of dry eye (in Spanish). *Arch Soc Esp Oftalmol.* 2002;77:493–500.
9. Belmonte C, Acosta MC, Schmelz M, Gallar J. Measurement of corneal sensitivity to mechanical and chemical stimulation with a CO_2 esthesiometer. *Invest Ophthalmol Vis Sci.* 1999;40:513–519.
10. Acosta MC, Belmonte C, Gallar J. Sensory experiences in humans and single-unit activity in cats evoked by polymodal stimulation of the cornea. *J Physiol.* 2001;534:511–525.
11. Acosta MC, Tan ME, Belmonte C, Gallar J. Sensations evoked by selective mechanical, chemical, and thermal stimulation of the conjunctiva and cornea. *Invest Ophthalmol Vis Sci.* 2001;42:2063–2067.
12. Yarnitsky D, Ochoa JL. Studies of heat pain sensation in man: perception thresholds, rate of stimulus rise reaction time. *Pain.* 1990;40:85–91.
13. Gallar J, Acosta MC, Moilanen JA, Holopainen JM, Belmonte C, Tervo TM. Recovery of corneal sensitivity to mechanical and chemical stimulation after laser in situ keratomileusis. *J Refract Surg.* 2004;20:229–235.
14. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2005;46:2341–2345.
15. Benítez-Del-Castillo JM, Acosta MC, Wassfi MA, et al. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2007;48:173–181.
16. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum.* 2004;50:2974–2984.
17. Chen X, Gallar J, Pozo MA, Baeza M, Belmonte C. CO_2 stimulation of the cornea: a comparison between human sensation and nerve activity in polymodal nociceptive afferents of the cat. *Eur J Neurosci.* 1995;7:1154–1163.
18. Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum.* 2003;48:1420–1429.
19. Staud R, Bovee CE, Robinson ME, Price DD. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain.* 2008;15:139:315–323.

20. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea.* 1998;17(6):584–589.
21. Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the pathophysiology of dry eye. *Exp Eye Res.* 2004;78(3):409–416.
22. de Paiva CS, Pflugfelder SC. Corneal epitheliopathy of dry eye induces hyperesthesia to mechanical air jet stimulation. *Am J Ophthalmol.* 2004;137:109–115.
23. Staud R. Treatment of fibromyalgia and its symptoms. *Expert Opin Pharmacother.* 2007;8:1629–1642.
24. Staud R. Are tender point injections beneficial: the role of tonic nociception in fibromyalgia. *Curr Pharm Des.* 2006;12:23–27.
25. Price DD, Staud R. Neurobiology of fibromyalgia syndrome. *J Rheumatol Suppl.* 2005;75:22–28.
26. Montoya P, Pauli P, Batra A, Wiedemann G. Altered processing of pain-related information in patients with fibromyalgia. *Eur J Pain.* 2005;9:293–303.
27. Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. *Nat Clin Pract Rheumatol.* 2006;2:90–98.
28. Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain.* 2006;124:242–263.