Biological Research for Nursing
2019, Vol. 21(4) 400-406

DOI: 10.1177/1099800419853633
journals.sagepub.com/home/brn
SAGE

The Relationship Between β-Endorphin and Experimental Pain Sensitivity in Older Adults With Knee Osteoarthritis

Hyochol Ahn, PhD, APRN, ANP-BC[1], Jun-Ho La, PhD[2], Jin M. Chung, PhD[2], Hongyu Miao, PhD[3], Chengxue Zhong, MS[3], Miyong Kim, PhD[4], Kyungeh An, PhD[5], Debra Lyon, PhD[6], Eunyoung Choi, RN[7], and Roger B. Fillingim, PhD[8]

Abstract

Osteoarthritis (OA) is the most common cause of pain in people aged ≥45 years, and the knee is the most commonly affected joint. There is a growing interest in understanding the biological factors that influence pain among older adults, but few studies have examined the relationship between β-endorphin and experimental pain sensitivity in older adults with knee OA pain. The purpose of this study was to investigate the relationship between resting plasma levels of β-endorphin and experimental pain sensitivity. This study was a secondary analysis of data for 40 adults with knee OA pain in whom quantitative sensory testing was used to measure experimental sensitivity to heat- and mechanically induced pain. The mean age of the sample was 60 years ($SD = 9$ years), and approximately half were female (53%). Regression analyses indicated that β-endorphin level was negatively related to pressure pain threshold ($\beta = -17.18$, $p = .02$) and positively related to punctate mechanical pain ($\beta = 17.13$, $p = .04$), after controlling for age, gender, and OA severity. We did not find a significant relationship between β-endorphin and heat pain tolerance. The results suggest that higher circulating levels of β-endorphin at rest are associated with increased sensitivity to mechanical pain in older adults with knee OA. These findings add to the literature regarding biological factors associated with pain sensitivity in older adults with chronic pain. Additional studies are needed to identify mediators of the relationship between β-endorphin and pain sensitivity in OA and other musculoskeletal pain conditions.

Keywords

osteoarthritis, β-endorphin, experimental pain sensitivity, quantitative sensory testing

Chronic pain affects 100 million people in the United States, with annual costs of up to $635 billion (Gaskin & Richard, 2012). Osteoarthritis (OA) is one of the leading causes of pain in older adults (Hunter, McDougall, & Keefe, 2008), with the knee being the most commonly affected joint (Wallace et al., 2017). Symptomatic knee OA affects more than 14 million U.S. adults (Deshpande et al., 2016).

Although knee OA has been historically conceptualized as a regional pain condition with symptoms driven by localized joint pathophysiology, increasing evidence demonstrates that knee OA pain is characterized by altered pain and sensory processing in the central nervous system (Lluch, Torres, Nijs, & Van Oosterwijck, 2014). Neuroimaging studies have revealed that alterations in pain-related central mechanisms are associated with OA pain (Hiramatsu et al., 2014), possibly due to enhanced excitability and efficiency of synapses in central pain pathways by continuous nociceptive input from structural joint changes in knee OA (Arendt-Nielsen, Skou, Nielsen, & Petersen, 2015).

[1] Department of Research, Cizik School of Nursing, University of Texas Health Science Center, Houston, TX, USA
[2] Department of Neuroscience, Cell Biology, and Anatomy, University of Texas Medical Branch, Galveston, TX, USA
[3] School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA
[4] School of Nursing, University of Texas at Austin, Austin, TX, USA
[5] Adult Health and Nursing Systems, Virginia Commonwealth University, Richmond, VA, USA
[6] College of Nursing, University of Florida, Gainesville, FL, USA
[7] Angels of Care Home Health, Houston, TX, USA
[8] Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL, USA

Corresponding Author:
Hyochol Ahn, PhD, APRN, ANP-BC, Department of Nursing Systems, Cizik School of Nursing, The University of Texas Health Science Center, 6901 Bertner Avenue, Ste. 567A, Houston, TX 77030, USA.
Email: hyochol.ahn@uth.tmc.edu

Nurse scientists have commonly adopted the biopsychosocial model of pain to address chronic pain. This model of pain hypothesizes that pain is dynamically affected by multidimensional factors (Fillingim, 2017) including biological, psychological, and social factors. Among the biological factors that may influence pain among older adults, researchers have suggested that β-endorphin, an endogenous opioid neuropeptide, is involved in pain sensation, but few studies have examined the relationship between circulating plasma β-endorphin at rest and experimental pain sensitivity in older adults with knee OA. β-endorphins are synthesized by innate and adaptive immune cells and by the anterior lobe of the pituitary gland, in which they are also stored (Plein & Rittner, 2018). They produce analgesia and immune response regulation by binding to μ-opioid receptors expressed in sensory neurons and immune cells (Sprouse-Blum, Smith, Sugai, & Parsa, 2010). Although β-endorphin in the cerebrospinal fluid and local inflamed tissues could inhibit pain perception via activation of opioid receptors in the central and peripheral nervous systems, respectively, the effect of resting plasma β-endorphin on analgesic pathways is not well understood (Bruehl, Burns, Chung, & Chont, 2012). Interestingly, some clinical studies have indicated that higher resting plasma β-endorphin levels are associated with higher acute pain intensity, suggesting that higher levels of plasma β-endorphin might reduce endogenous opioid analgesia (Matejec, Ruwoldt, Bodeker, Hempelmann, & Teschemacher, 2003). Therefore, the purpose of this study was to examine the relationship between resting plasma β-endorphin level and experimental pain sensitivity in older adults with knee OA pain.

Materials and Methods

This study is a secondary analysis of baseline data from a research study carried out at the University of Florida Institute on Aging. Detailed selection criteria and enrollment procedures have been published and described previously (Ahn et al., 2017). Researchers recruited a total of 40 participants with knee OA pain, diagnosed according to American College of Rheumatology criteria (Altman et al., 1986), who ranged in age from 50 to 70 years, in North Central Florida via fliers posted around local educational institutions and in the community. Exclusion criteria included a serious medical illness (e.g., uncontrolled hypertension, heart failure, acute myocardial infarction), peripheral neuropathy, systemic rheumatic disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, or fibromyalgia), daily use of prescribed pain medicines, alcohol/substance abuse, cognitive impairment, and hospitalization within the preceding year for psychiatric illness. All participants gave oral and written informed consent prior to participation, and the university's institutional review board approved all procedures.

Procedures

Following informed consent, participants provided demographic and background information including age, gender, ethnicity, and OA severity. Participants indicated the knee in which they experienced the most severe pain, which served as the index knee. Investigators took weight-bearing radiographs of both knees for all participants and determined OA severity using the Kellgren–Lawrence score (Scott et al., 1993). The Kellgren–Lawrence system is the most widely used clinical tool for the radiographic diagnosis of osteoarthritis using five grades: Grade 0 (no radiographic features of OA are present), Grade 1 (doubtful joint space narrowing and possible osteophytic lipping), Grade 2 (definite osteophytes and possible joint space narrowing on anteroposterior weight-bearing radiograph), Grade 3 (multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity), and Grade 4 (large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity; Kellgren & Lawrence, 1957; Kohn, Sassoon, & Fernando, 2016).

After collection of demographic and background information, researchers drew a 6-ml blood sample from each participant by venipuncture according to a standard phlebotomy protocol and processed and stored blood specimens for assay as described below. The Clinical Research and Metabolism and Translational Science Core in the University of Florida's Claude D. Pepper Older Americans Independence Center performed the assays. Participants next received multimodal quantitative sensory testing to measure experimental pain sensitivity including heat pain tolerance, pressure pain threshold, and punctate mechanical pain.

Measures

β-endorphin. Investigators drew 6 ml of blood into ethylenediaminetetraacetic acid plasma tubes. Samples were inverted 5 times and kept on ice. Aprotinin was added (0.6 trypsin inhibitor units [TIU]/ml of blood), and the tubes were gently mixed several times to inhibit activity of proteinases. Within 30 min of collection, samples were centrifuged at 1,600 rpm for 15 min at 4 °C, aliquoted, and immediately stored in a −80 °C freezer. Solid-phase extraction of plasma samples was performed using an Oasis HLB (30 mg) 96-well plate along with a vacuum manifold (Waters Corporation, Milford, MA), following the manufacturer's recommendations. Briefly, the plate was conditioned with acetonitrile and equilibrated 2 times with 0.1% trifluoroacetic acid (TFA) in high-performance liquid chromatography (HPLC)–grade water. Samples were acidified with 1% TFA (1:1) and loaded onto the plate. The plate was washed 3 times with 0.1% TFA in HPLC-grade water. Samples were eluted in 60% acetonitrile/40% HPLC-grade water/0.1% TFA and dried in a Savant AES1010 Automatic Environmental SpeedVAC w/VaporNet Radiant Cover. Samples were reconstituted to the original sample volume in assay buffer. β-endorphin was measured in the extracted plasma samples with an enzyme immunoassay method using a commercial kit (cat. no. EK-022-14; Phoenix Pharmaceutical, Belmont, CA). The intra- and interassay variation coefficients were <6.5% and <10%, respectively.

Experimental pain sensitivity. Heat pain tolerance was measured on both the index knee (most painful knee) and the ipsilateral ventral forearm with contact heat stimuli delivered via a Medoc TSA-II neurosensory analyzer (Ramat Yishai, Israel) using an ascending method of limits. From a baseline of 32 °C, the thermode temperature increased at a rate of 0.5 °C/s until participants responded by pressing a button on a handheld device when they no longer felt able to tolerate the pain. Researchers conducted three trials of heat pain tolerance at each of the two locations, and the temperatures of the three individual trials were averaged to generate heat pain tolerance at each site.

Researchers assessed two types of mechanical pain responses: pressure pain thresholds and punctate mechanical pain. First, pressure pain thresholds were measured by using a handheld digital pressure algometer (Wagner, Greenwich, CT) to apply blunt mechanical pressure to deep tissues (i.e., muscle and joint). The pressure increased at a rate of 0.3 kgf/cm^2/s until participants notified the experimenter when the sensation first became painful. Pressure pain thresholds were assessed at four sites: the medial and lateral aspects of the index knee, ipsilateral quadriceps, and trapezius. Investigators conducted three trials of pressure pain tolerance at each of the four locations and averaged the results of the three individual trials to generate pressure pain threshold at each site.

Following the assessment of the pressure pain threshold, researchers measured punctate mechanical pain sensitivity with a calibrated nylon monofilament, delivering a target force of 300*g* to assess participants' cutaneous mechanical sensitivity to punctate stimuli on both the index patella and the dorsal aspect of the ipsilateral hand. Numerical pain intensity ratings were rated on a scale of 0 (*no pain sensation*) to 100 (*the most intense pain sensation imaginable*) following 10 contacts at a rate of one contact per second at each of the two locations. This procedure was performed twice at each site, and pain ratings for the two individual trials were averaged to generate the punctate mechanical pain following 10 contacts at each site.

Statistical Analyses

All statistical analyses were performed with SAS Version 9.4. For purposes of variable reduction, we created composite measures of pain sensitivity. First, we used the Shapiro–Wilk test to determine the normality of data distribution for the experimental pain sensitivity measures. Normality was supported for each of the three measures. We then calculated *z* scores for the heat pain tolerance measurements at the arm and knee; the pressure pain threshold measures at the medial knee, lateral knee, quadriceps, and trapezius; and the punctate pain measurements at the patella and hand. The *z* scores for each pain measure were averaged across body sites to generate overall values of heat pain tolerance, pressure pain threshold, and punctate mechanical pain for variable reduction, placing all pain measures on a common metric without altering the distributional characteristics of the underlying data. This technique is commonly used in experimental pain research (Cardoso et al., 2016; Cruz-Almeida & Fillingim, 2014). These *z* scores were applied as outcomes for study of their relationships with β-endorphin. Gender, age, and OA severity were used to fit linear regression models for each experimental pain measure. SAS PROC GLM was used for parameter estimations after fixing the gender, age, and OA severity in our model.

Table 1. Demographic and Clinical Characteristics of Participants.

Characteristic	Value
Age, years, mean (*SD*)	59.9 (9.13)
Gender, female, *n* (%)	21 (52.5)
Race, *n* (%)	
White	20 (50.0)
Other	20 (50.0)
Education, *n* (%)	
High school	6 (15.0)
2-year college	7 (17.5)
4-year college	12 (30.0)
Master's degree	6 (15.0)
Doctoral degree	9 (22.0)
BMI, kg/m^2, mean (*SD*)	26.0 (3.2)
Resting plasma β-endorphin, ng/ml, mean (*SD*)	0.04 (0.02)
Heat pain tolerance, °C, mean (*SD*)[a]	45.55 (3.07)
Pressure pain threshold, kPa, mean (*SD*)[a]	2.83 (1.12)
Punctate pain, mean (*SD*)[a]	39.13 (25.25)
Kellgren–Lawrence radiographic score, *n* (%)	
Grade 0	13 (32.5)
Grade 1	8 (20.0)
Grade 2	10 (25.0)
Grade 3	8 (20.0)
Grade 4	1 (2.5)

Note. $N = 40$. BMI = body mass index; *SD* = standard deviation.
[a]Overall average score.

Results

Demographic Characteristics

Of the 40 participants, approximately half (52.5%) were female, and the mean age of participants was 59.9 years ($SD = 9.1$). The mean concentration of β-endorphin was 0.04 ng/ml ($SD = 0.02$), and the mean body mass index in the sample was 26.50 kg/m^2 ($SD = 3.17$; see Table 1).

Relationship Between β-Endorphin and Experimental Pain Sensitivity

There was a significant relationship between β-endorphin level and mechanical pain including both pressure pain threshold and punctate pain (see Table 2). β-endorphin was negatively related to pressure pain threshold ($\beta = -17.18$, $t = -2.40$, $p = .02$) and positively related to punctate mechanical pain ($\beta = 17.13$, $t = 2.14$, $p = .04$), after controlling for age, gender, and OA severity. There was no significant relationship between β-endorphin and heat pain tolerance.

Table 2. Results of Regression Model.

Variable	β	*SE*	*t* Value	*p* Value
Heat pain tolerance[a]				
β-endorphin	−7.54	7.61	−0.99	.33
Age	−0.02	0.02	−0.97	.34
Female	−0.64	0.25	−2.54	.02
OA severity	0.35	0.13	2.68	.01
Pressure pain threshold[a]				
β-endorphin	−17.18	7.16	−2.40	.02
Age	−0.01	0.02	−0.68	.50
Female	−0.90	0.24	−3.80	<.01
OA severity	0.09	0.12	0.77	.45
Punctate pain[a]				
β-endorphin	17.13	8.01	2.14	.04
Age	−0.01	0.02	−0.28	.78
Female	0.09	0.26	0.34	.74
OA severity	−0.20	0.13	−1.44	.16

Note. OA = osteoarthritis. R^2 heat pain tolerance = .34, pressure pain threshold = .39, punctate pain = .26.
[a]Average z score.

Discussion

This study was designed to examine the relationship between β-endorphin and pain sensitivity among older adults with knee OA. We found that higher circulating β-endorphin levels at rest were associated with increased sensitivity to mechanical pain (i.e., lower pressure pain threshold and higher punctate pain ratings) in older adults with knee OA. The mean concentration of β-endorphin in this study was 0.04 ng/ml, which is similar to that reported for healthy elderly individuals in other reports (Rolandi et al., 1987). We also found that female participants had a lower heat pain tolerance and pressure pain threshold. To our knowledge, this study is the first to investigate resting-state plasma β-endorphin levels in relation to pain sensitivity in patients with knee OA.

A number of studies have suggested that β-endorphin is involved in endogenous opioid analgesia (Feldreich, Ernberg, Lund, & Rosen, 2012). However, other reports have shown that higher plasma β-endorphin levels are related to elevated pain, which aligns with our findings. For example, Bruehl, Burns, Chung, and Chont (2012) found that higher resting plasma β-endorphin levels were associated with greater reported pain intensity in healthy adults and to reduced endogenous opioid analgesic capacity among adults with low-back pain. Similarly, Heddini et al. (2014) found a positive relationship between resting plasma levels of β-endorphin and the number of concomitant pain symptoms among women with vestibulodynia. In addition, Leonard, Klem, Asher, Rapoff, and Leff (1993) reported that serum β-endorphin level was positively associated with self-reported pain-intensity scores in postoperative patients.

The exact mechanisms underlying the positive relationship between circulating plasma β-endorphin level at rest and higher pain sensitivity are not clear. Any attempt to interpret this finding must account for the possibility that the plasma β-endorphin level is not necessarily correlated with the level of β-endorphin in the central nervous system, where the endogenous opioid peptide is a key component in the descending pain modulatory system (Basbaum & Fields, 1984). Houghten, Swann, and Li (1980) found that β-endorphin in systemic circulation was not significantly taken up into the central nervous system and that hypophysectomy, which dramatically decreased plasma levels of β-endorphin, affected its levels in the brain only slightly. One possible explanation for the association between higher pain sensitivity and higher resting plasma levels of β-endorphin is that elevated resting plasma β-endorphin might be an indicator for reduced endogenous opioid analgesic capacity potentially due to downregulation of the opioid receptors (Bruehl et al., 2012). In animal models of chronic neuropathic pain, the μ-opioid receptor is downregulated, decreasing the therapeutic efficacy of opioid analgesics (Niikura, Narita, Butelman, Kreek, & Suzuki, 2010). β-endorphin appears to play a pivotal role in such downregulation as evidenced by the finding that mutant mice lacking β-endorphin do not show a decrease in the analgesic efficacy of morphine or an increase in the μ-opioid receptor phosphorylation leading to desensitization and internalization of the receptor after neuropathic injury (Petraschka et al., 2007). As previous studies have shown that chronic arthritis also downregulates μ-opioid receptor expression in rats, resulting in the loss of inhibitory effect of endomorphin-1 on the excitability of sensory fibers innervating the inflamed joint (Li, Proud, Zhang, Wiehler, & McDougall, 2005), it could be that OA patients with higher resting β-endorphin levels have more prominent downregulation of the μ-opioid receptor, leading to greater pain sensitivity.

Another possible explanation for the positive correlation between the resting plasma β-endorphin levels and mechanical pain sensitivity is that in chronic inflammatory pain conditions, plasma β-endorphin may perform a pronociceptive function for the sensory nervous system. For example, in an animal model of chronic inflammatory bowel disease, normally inhibitory opioid signaling (inhibitory G protein-mediated) became excitatory (protein kinases A- and C-mediated) in primary afferent neurons when the animals were under experimental stress or the neurons were incubated with the stress hormones epinephrine and corticosterone (Guerrero-Alba et al., 2017). Therefore, it would be of interest in future research to determine whether the levels of stress hormones in OA patients influence the degree of correlation between pain sensitivity and β-endorphin levels.

Unlike mechanical pain sensitivity, heat pain sensitivity showed no correlation with the resting plasma β-endorphin levels in the OA patients. It is unclear how the potentially reduced/reversed analgesic function of β-endorphin selectively affects mechanical pain sensitivity. Notably, endogenous opioids have been found to affect only mechanical, and not heat, hypersensitivity in chronic neuropathic pain models (Labuz, Celik, Zimmer, & Machelska, 2016), suggesting that endogenous opioid peptides, unlike exogenous opioid analgesics, may differentially influence sensory pathways of different

modalities in chronic pain conditions. In other words, mechano- and heat-sensitive afferents could have different responsiveness to plasma β-endorphin. Therefore, it is not unlikely that OA patients with a dysfunctional endogenous opioid system may manifest a modality-specific pain hypersensitivity in quantitative sensory testing.

Limitations

This study's results should be interpreted in light of several limitations. First, the data collection was based on a cross-sectional design, consequently limiting our ability to draw any conclusions about causal relationships. Second, given the small sample size, we restricted consideration of confounding variables to pain-related individual factors only, including age, gender, and OA severity. Finally, the time of collection of blood sample was not limited to a specific time window during the day, so there could have been variation due to effects of circadian rhythm on endorphin secretion among participants. The plasma level of β-endorphin is typically high in the early morning and gradually decreases until midnight in younger adults (Sekiya, Nawata, Kato, Motomatsu, & Ibayashi, 1986), but such circadian variation is not obvious in the elderly (Rolandi et al., 1987).

Implications for Nursing Practice and Research

The findings of this study have potential clinical implications for chronic pain management in nursing and health care. Health-care providers might consider that persons with higher resting plasma β-endorphin levels are more likely to have inadequate endogenous antinociceptive molecular activity. In particular, older adults with chronic painful conditions (e.g., OA) who have higher resting plasma β-endorphin levels may need more appropriate pain management. The findings might thus promote nurses' awareness of individual variations in pain and pain-management response when they assess patients' pain and evaluate the effectiveness of pain-management interventions. By considering individual variation, the precision of pain management can be significantly improved.

The further identification of molecular markers associated with pain sensitivity, including β-endorphin, would advance the science of pain and pain management by specifying the biological pathways of pain sensitivity in chronic pain disorders. Further exploration of the role of β-endorphin in additional studies is warranted given the preliminary evidence in multiple studies of its role in pain sensitivity across chronic pain populations. In the future, this knowledge could lead to additional therapeutic targets for pain reduction including targeted pharmacologic and complementary and alternative therapies.

The findings from the present study also provide a foundation for future research in nursing and symptoms sciences to investigate the mechanisms by which resting plasma β-endorphin influences pain sensitivity. First, conduct of an extended study with a larger sample should validate our findings. A comparison of the associations between biomarkers and pain sensitivity between healthy individuals and patients with knee OA would reveal whether our findings are generalizable to healthy adults or are specific to adults with knee OA. Second, future studies are needed to investigate differences between plasma β-endorphin and β-endorphin in the cerebrospinal fluid or μ-opioid receptor binding in the brain. Finally, future studies that incorporate additional biological and psychological measures are needed to elucidate underlying mechanisms in chronic pain conditions.

Conclusion

Reports regarding the relationship between β-endorphin and pain sensitivity have been inconsistent, and the relationship between resting plasma levels of β-endorphin and pain sensitivity in older adults with chronic pain is therefore not well understood. The results of the present study suggest that higher plasma levels of β-endorphin may be associated with heightened mechanical pain sensitivity among older adults with knee OA pain. The study adds to the growing literature regarding the relationship between biological markers and pain sensitivity. Further investigation is needed to advance our understanding of the underlying mechanism of β-endorphin in chronic pain in OA and other musculoskeletal pain conditions.

Acknowledgments

The authors wish to thank Christiaan Leeuwenburgh, Brian Bouverat, Jini Curry, Marvin Dirain (Institute on Aging, University of Florida, Gainesville), and Setor Sorkpor for their technical assistance with the extractions and enzyme immunoassays.

Author Contributions

Hyochol Ahn contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Jun-Ho La contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Jin M. Chung contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Hongyu Miao contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Chengxue Zhong contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Miyong Kim contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Kyungeh An contributed to design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Debra Lyon contributed to conception, design, acquisition, analysis, and interpretation; drafted the

manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Eunyoung Choi contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Roger B. Fillingim contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the National Institutes of Health/National Institute on Aging Claude D. Pepper Older American's Independence Center (P30 AG028740).

ORCID iD

Hyochol Ahn https://orcid.org/0000-0002-9998-4876

References

Ahn, H., Woods, A. J., Kunik, M. E., Bhattacharjee, A., Chen, Z., Choi, E., & Fillingim, R. B. (2017). Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimulation*, *10*, 902–909.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., ... Hochberg, M. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and Rheumatism*, *29*, 1039–1049.

Arendt-Nielsen, L., Skou, S. T., Nielsen, T. A., & Petersen, K. K. (2015). Altered central sensitization and pain modulation in the CNS in chronic joint pain. *Current Osteoporosis Reports*, *13*, 225–234. doi:10.1007/s11914-015-0276-x

Basbaum, A. I., & Fields, H. L. (1984). Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience*, *7*, 309–338. doi:10.1146/annurev.ne.07.030184.001521

Bruehl, S., Burns, J. W., Chung, O. Y., & Chont, M. (2012). What do plasma beta-endorphin levels reveal about endogenous opioid analgesic function? *European Journal of Pain*, *16*, 370–380. doi:10.1002/j.1532-2149.2011.00021.x

Cardoso, J. S., Riley, J. L., 3rd, Glover, T., Sibille, K. T., Bartley, E. J., Goodin, B. R., ... Cruz-Almeida, Y. (2016). Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis. *Pain*, *157*, 2104–2114. doi:10.1097/j.pain.0000000000000625

Cruz-Almeida, Y., & Fillingim, R. B. (2014). Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Medication*, *15*, 61–72. doi:10.1111/pme.12230

Deshpande, B. R., Katz, J. N., Solomon, D. H., Yelin, E. H., Hunter, D. J., Messier, S. P., ... Losina, E. (2016). Number of persons with symptomatic knee osteoarthritis in the US: Impact of race and ethnicity, age, sex, and obesity. *Arthritis Care & Research (Hoboken)*, *68*, 1743–1750. doi:10.1002/acr.22897

Feldreich, A., Ernberg, M., Lund, B., & Rosen, A. (2012). Increased beta-endorphin levels and generalized decreased pain thresholds in patients with limited jaw opening and movement-evoked pain from the temporomandibular joint. *Journal of Oral and Maxillofacial Surgery*, *70*, 547–556. doi:10.1016/j.joms.2011.09.013

Fillingim, R. B. (2017). Individual differences in pain: Understanding the mosaic that makes pain personal. *Pain*, *158*, S11–S18. doi:10.1097/j.pain.0000000000000775

Gaskin, D. J., & Richard, P. (2012). The economic costs of pain in the United States. *Journal of Pain*, *13*, 715–724. doi:10.1016/j.jpain.2012.03.009

Guerrero-Alba, R., Valdez-Morales, E. E., Jimenez-Vargas, N. N., Lopez-Lopez, C., Jaramillo-Polanco, J., Okamoto, T., ... Vanner, S. J. (2017). Stress activates pronociceptive endogenous opioid signalling in DRG neurons during chronic colitis. *Gut*, *66*, 2121–2131. doi:10.1136/gutjnl-2016-311456

Heddini, U., Johannesson, U., Gronbladh, A., Nyberg, F., Nilsson, K. W., & Bohm-Starke, N. (2014). A118G polymorphism in the mu-opioid receptor gene and levels of beta-endorphin are associated with provoked vestibulodynia and pressure pain sensitivity. *Scandinavian Journal of Pain*, *5*, 10–16. doi:10.1016/j.sjpain.2013.10.004

Hiramatsu, T., Nakanishi, K., Yoshimura, S., Yoshino, A., Adachi, N., Okamoto, Y., ... Ochi, M. (2014). The dorsolateral prefrontal network is involved in pain perception in knee osteoarthritis patients. *Neuroscience Letters*, *581*, 109–114. doi:10.1016/j.neulet.2014.08.027

Houghten, R. A., Swann, R. W., & Li, C. H. (1980). beta-Endorphin: Stability, clearance behavior, and entry into the central nervous system after intravenous injection of the tritiated peptide in rats and rabbits. *Proceedings of the National Academy of Sciences of the United States of America*, *77*, 4588–4591.

Hunter, D. J., McDougall, J. J., & Keefe, F. J. (2008). The symptoms of osteoarthritis and the genesis of pain. *Rheumatic Diseases Clinics of North America*, *34*, 623–643. doi:10.1016/j.rdc.2008.05.004

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Annals of the Rheumatic Diseases*, *16*, 494–502.

Kohn, M. D., Sassoon, A. A., & Fernando, N. D. (2016). Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. *Clinical Orthopaedics and Related Research*, *474*, 1886–1893. doi:10.1007/s11999-016-4732-4

Labuz, D., Celik, M. O., Zimmer, A., & Machelska, H. (2016). Distinct roles of exogenous opioid agonists and endogenous opioid peptides in the peripheral control of neuropathy-triggered heat pain. *Scientific Reports*, *6*, 32799. doi:10.1038/srep32799

Leonard, T. M., Klem, S. A., Asher, M. A., Rapoff, M. A., & Leff, R. D. (1993). Relationship between pain severity and serum

beta-endorphin levels in postoperative patients. *Pharmacotherapy*, *13*, 378–381.

Li, Z., Proud, D., Zhang, C., Wiehler, S., & McDougall, J. J. (2005). Chronic arthritis down-regulates peripheral mu-opioid receptor expression with concomitant loss of endomorphin 1 antinociception. *Arthritis and Rheumatism*, *52*, 3210–3219. doi:10.1002/art.21359

Lluch, E., Torres, R., Nijs, J., & Van Oosterwijck, J. (2014). Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *European Journal of Pain*, *18*, 1367–1375. doi:10.1002/j.1532-2149.2014.499.x

Matejec, R., Ruwoldt, R., Bodeker, R. H., Hempelmann, G., & Teschemacher, H. (2003). Release of beta-endorphin immunoreactive material under perioperative conditions into blood or cerebrospinal fluid: Significance for postoperative pain? *Anesthesia and Analgesia*, *96*, 481–486.

Niikura, K., Narita, M., Butelman, E. R., Kreek, M. J., & Suzuki, T. (2010). Neuropathic and chronic pain stimuli downregulate central mu-opioid and dopaminergic transmission. *Trends in Pharmacological Sciences*, *31*, 299–305. doi:10.1016/j.tips.2010.04.003

Petraschka, M., Li, S., Gilbert, T. L., Westenbroek, R. E., Bruchas, M. R., Schreiber, S., . . . Chavkin, C. (2007). The absence of endogenous beta-endorphin selectively blocks phosphorylation and desensitization of mu opioid receptors following partial sciatic nerve ligation. *Neuroscience*, *146*, 1795–1807. doi:10.1016/j.neuroscience.2007.03.029

Plein, L. M., & Rittner, H. L. (2018). Opioids and the immune system—friend or foe. *British Journal of Pharmacology*, *175*, 2717–2725. doi:10.1111/bph.13750

Rolandi, E., Franceschini, R., Marabini, A., Messina, V., Cataldi, A., Salvemini, M., & Barreca, T. (1987). Twenty-four-hour beta-endorphin secretory pattern in the elderly. *Acta Endocrinologica*, *115*, 441–446.

Scott, W. W., Jr., Lethbridge-Cejku, M., Reichle, R., Wigley, F. M., Tobin, J. D., & Hochberg, M. C. (1993). Reliability of grading scales for individual radiographic features of osteoarthritis of the knee. The Baltimore longitudinal study of aging atlas of knee osteoarthritis. *Investigative Radiology*, *28*, 497–501.

Sekiya, K., Nawata, H., Kato, K., Motomatsu, T., & Ibayashi, H. (1986). Diurnal rhythms of proopiomelanocortin-derived N-terminal peptide, beta-lipotropin, beta-endorphin and adrenocorticotropin in normal subjects and in patients with Addison's disease and Cushing's disease. *Endocrinologia Japonica*, *33*, 713–719.

Sprouse-Blum, A. S., Smith, G., Sugai, D., & Parsa, F. D. (2010). Understanding endorphins and their importance in pain management. *Hawaii Medical Journal*, *69*, 70–71.

Wallace, I. J., Worthington, S., Felson, D. T., Jurmain, R. D., Wren, K. T., Maijanen, H., . . . Lieberman, D. E. (2017). Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proceedings of the National Academy of Sciences of the United States of America*, *114*, 9332–9336. doi:10.1073/pnas.1703856114