Central nervous system monoaminergic activity in hip osteoarthritis patients with disabling pain: associations with pain severity and central sensitization

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Abstract

Introduction: Monoaminergic activity modulates nociceptive transmission in the central nervous system (CNS). Although pain is the most disabling symptom of osteoarthritis (OA), limited knowledge exists regarding the CNS mechanisms that amplify pain and drive sensitization processes in humans.

Objectives: The main objective of this study was to evaluate associations between cerebrospinal fluid (CSF) monoamine metabolites, pain severity, and central sensitization in patients with OA undergoing total hip arthroplasty (THA).

Methods: Patients with OA (n = 52) and pain-free controls (n = 30) provided CSF samples for measurement of serotonin (5-hydroxyindoleacetic acid [5-HIAA]), noradrenaline (3-methoxy-4-hydroxyphenylglycol [HMPG]), and dopamine (homovanillic acid [HVA]) monoamine metabolites. Patients with OA completed longitudinal evaluation of pain using clinical measures and quantitative sensory testing.

Results: Patients with OA had higher HMPG levels when compared with controls ($P = 0.036$). Within patients with OA undergoing THA, higher 5-HIAA and HVA levels were consistently associated with higher preoperative pain severity. Higher concentrations of 5-HIAA and HVA were also associated with lower conditioned pain modulation levels, whereas higher HMPG levels were linked to more efficient conditioned pain modulation. Patients with higher levels of CSF HVA exhibited increased pressure pain sensity (arm pressure pain detection threshold < 250 kPa vs ≥ 250 kPa, $P = 0.042$). Higher preoperative levels of CSF 5-HIAA predicted poorer pain control 6 months postoperatively (brief pain inventory pain severity; adjusted $\beta = 0.010$, 95% CI 0.001–0.019).

Conclusions: In OA patients with disabling pain, higher CSF levels of serotonin and dopamine metabolites are associated with increased pain severity and central sensitization. Increased noradrenergic activity may be associated with more efficient pain inhibitory capacity.

Keywords: Monoamines, Cerebrospinal fluid, Central nervous system, Osteoarthritis, Pain, Central sensitization

1. Introduction

Osteoarthritis (OA) remains a leading cause of global disability and morbidity, with increasing prevalence in aging populations.[22,39]

Given the rapidly growing rates of disability due to OA, surgical volumes of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in the United States are estimated to increase more than 70% over the next 10 years.[42] Pain is the most prominent

symptom of OA,[7] and almost 1 in 5 patients awaiting THA report a health state worse than death.[41] Although many patients with OA may benefit from joint replacement surgery, up to 23% of patients with hip OA and 10% to 34% of patients with knee OA experience unfavorable long-term postoperative pain outcomes.[6]

Central sensitization, ie, mechanisms in the central nervous system (CNS) that amplify pain, influences the development and maintenance of persistent pain states. Features of central sensitization, eg, widespread pain hypersensitivity, are common among patients with OA,[18,45] and chronic pain populations (including OA) demonstrate impaired conditioned pain modulation (CPM),[3,26,27] which reflects decreased endogenous pain inhibitory capacity. In pain associated with OA, central sensitization correlates with clinical pain severity,[3,17,49] and preoperative temporal summation (CNS enhancement of pain caused by repeated noxious stimulation) predicts chronic postsurgical pain (CPSP).[37] Despite these salient links between central sensitization and dysregulation of pain perception in OA, limited knowledge exists regarding CNS mechanisms that drive and augment pain sensitization.

Descending pain modulating influences on spinal nociceptive processing mainly involve opioidergic and monoaminergic signaling, originating from midbrain (periaqueductal gray [PAG]) and medullary structures (rostral ventromedial medulla [RVM] and subnucleus reticularis dorsalis).[31] In experimental models, dysregulation of monoaminergic activity at supraspinal and spinal sites, including PAG and RVM, contribute to pain behavior. For example, long-term neuropathic pain is associated with increased expression and sensitivity of α_2-adrenoceptors in the locus coeruleus, which is the main source of noradrenaline in the CNS.[1] As neuropathic pain progresses, noradrenergic pathways undergo further neuroplastic changes that may impair pain inhibitory effects.[28] Whereas pain modulatory effects of serotonin are complex and depend on activation of various receptor subtypes, it seems that alterations in serotonergic activity lead to increased central sensitization. For example, pain facilitatory 5-HT receptors, such as the 5-HT2A receptor, are upregulated in the CNS in models of persistent neuropathic and inflammatory pain.[12] Maladaptive dopaminergic neuroplastic changes, eg, decreases in D2 receptor expression in the nucleus accumbens, are also observed in neuropathic pain models.[40] Notably, drugs that target and enhance these monoaminergic systems, such as amitriptyline and serotonin noradrenaline reuptake inhibitors (SNRIs), provide clinically meaningful analgesia across several persistent pain conditions.[12,19]

Previously, only limited effort has been directed towards assessment of monoaminergic neurotransmission and neurophysiological characteristics in humans.[33] In this investigation of patients with disabling hip OA pain, we examined the relationship between CNS monoaminergic activity—using cerebrospinal fluid (CSF) monoamine metabolites—pain ratings, and quantitative sensory testing (QST) measures of central sensitization and pain inhibitory capacity. In addition, we evaluated whether preoperative levels of CSF monoamine (dopamine, serotonin, and noradrenaline) metabolites were associated with long-term pain outcomes after THA.

2. Methods

2.1. Study design

These analyses were completed on data from a prospective, observational study (neuro pain sleep immunology, neuroPSI). We first cross-sectionally evaluated differences in CSF monoamine metabolites between patients with disabling hip OA pain and pain-free controls. Second, in a longitudinal design focused on patients with OA undergoing THA, we examined the associations between monoaminergic activity in the CNS and clinical pain ratings, objective measures of central sensitization, and long-term pain control after THA. Based on preclinical findings,[12,15,32,47,50] we hypothesized that higher preoperative serotonergic activity would be associated with increased pain severity, central sensitization, and poorer postoperative pain control. Analyses of CSF neuroinflammatory mediators in this cohort have already been published.[8]

Study approval was obtained from the Regional Ethics Committee (Dnr 2018/396 and Dnr 2008/290). All participants provided written informed consent before study activities.

2.2. Subjects

2.2.1. Patients with osteoarthritis

Consecutive adult patients scheduled to undergo primary THA because of disabling OA pain were screened and assessed for eligibility through chart review and structured interview. Participants were considered for inclusion if they had experienced OA-related pain ≥12 months with mean pain intensity numerical rating scale (NRS) score ≥4. Exclusion criteria entailed factors that may confound assessment of biomarkers in the CSF, most importantly, acute illness, malignancy, immunomodulating treatment, neurological or severe psychiatric disorders, cognitive impairment, and American Society of Anesthesiology (ASA) physical status classification >3. Seventy-nine patients were screened for participation; after application of inclusion/exclusion criteria, 52 patients were eligible and consented to study activities (as previously described).[8]

2.2.2. Pain-free, healthy controls

Healthy controls (n = 30) were recruited from a separate study, focusing on CSF inflammatory mediators in Parkinson disease.[24] In addition to exclusion criteria stated earlier for patients with OA, controls were excluded if they reported any type of ongoing pain problems or presented a diagnosis associated with persistent pain. To confirm absence of exclusion criteria, all controls underwent comprehensive neurological examination and cognitive testing before enrollment.

2.3. Procedures

Patients with OA underwent THA at the Department of Orthopedics, Hässleholm Hospital, where the highest annual volume of THAs has been conducted in Sweden since 2002. Modality of surgery has previously been described.[8] Spinal anesthesia was administered to all patients (hyperbaric bupivacaine). In brief, the perioperative care is standardized and adheres to principles of enhanced recovery after surgery, including elements such as early mobilization (already on the day of surgery), multimodal pain control (1 g of paracetamol 3 times daily until postoperative day [POD]7, 200 mg of celecoxib twice daily until POD3, and oxycodone as needed), and early hospital discharge (average length of stay, 1.7 days).

2.3.1. Questionnaires

As previously reported,[8] patients with OA were characterized preoperatively through multiple questionnaires, including the Brief

Pain Inventory-Short Form (BPI-SF),[16] Douleur Neuropathique (DN)-4,[11] European Quality of Life-5 Dimensions (EQ-5D),[25] Hospital Anxiety and Depression Scale (HADS),[51] Insomnia Severity Index (ISI),[4] Pittsburgh Sleep Quality Index (PSQI),[14] and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC OA).[5] Pain-related and OA-related questionnaires were not applicable to the control participants.

In addition to baseline preoperative questionnaires, patients with OA underwent postoperative pain assessment through telephone on POD7 (BPI-SF) and at 3 and 6 months postoperatively (BPI-SF, WOMAC OA pain score).

2.3.2. Assessment of pain neurophysiology in patients with osteoarthritis

The QST protocol has previously been outlined in detail.[8] All testing was conducted approximately 1 hour before spinal anesthesia/CSF sampling. The protocol pertaining to assessment of central sensitization is described further. All QST was performed by one physician (M.F.B.) in a calm, air-conditioned room separate from the operating department.

2.3.2.1. Arm pressure pain threshold

For the assessment of arm pressure pain detection thresholds (PPDTs), a digital pressure algometer with a 1 cm^2 hard rubber probe was applied to a proximal, volar area of the nondominant forearm at increasing pressure intensities of 20 kPa/s (SBMEDIC Electronics, Solna, Sweden). Subjects were instructed to push a button when the pressure was first perceived as painful. The PPDT was calculated as the average of 3 trials with an interstimulus interval of 30 seconds. Previous findings show that remote site arm PPDTs below 250 kPa possibly indicate central sensitization in patients with OA.[8,29,48]

2.3.2.2. Conditioned pain modulation

Baseline assessment of nondominant arm PPDT was performed before CPM testing. The CPM conditioning stimulus was achieved through a 12-cm wide occlusion cuff placed approximately 2 cm proximal to the cubital fossa on the dominant arm. The cuff was gradually inflated in increments of 10 to 15 mm Hg, until the subject confirmed a pressure pain intensity level 5/10 (0 = no pain, 10 = worst imaginable pain); this moderate level of arm occlusion cuff conditioning pain intensity has previously been shown to evoke CPM effects.[43] During maintenance of the conditioning stimulus, PPDT was reassessed on the nondominant arm. Three CPM trials were completed, and the CPM effect was calculated as average absolute value ($PPDT_{conditioning} - PPDT_{baseline}$) and percentage: $((PPDT_{conditioning} - PPDT_{baseline})/PPDT_{baseline}) \times 100$.

2.3.2.3. Temporal summation in the area of maximum pain

Monofilament probes were used to assess mechanical temporal summation in the area indicated as most painful in the OA-affected joint. First, subjects rated the pain response to a single punctate stimulus of a monofilament calibrated to exert a force of 588 mN (0–100; 0 = no pain, 100 = worst pain imaginable). Second, 10 repeated punctate stimuli at a rate of 1 Hz were administered within an area of 1 cm^2, whereafter subjects were asked to rate their peak pain intensity during the stimulation period. Temporal summation was calculated as peak pain rating divided by initial pain rating of single stimulus. In addition,

aftersensations such as paresthesias and numbness, lasting more than 30 seconds after completion of the testing, were recorded.

2.3.3. Sampling of cerebrospinal fluid

Immediately before administration of spinal anesthesia, 10 mL of CSF was collected in 5 mL Protein LoBind Tubes (Eppendorf AG, Hamburg, Germany). To reduce circadian influences on CSF biomarkers, all samples were acquired from 8 AM to 12 PM. All CSF samples were centrifuged at 2000g for 10 minutes at 4°C and stored in 1 mL aliquots at −80°C before a batch analysis.

2.3.4. Assessment of monoamine metabolites: high-performance liquid chromatography

Cerebrospinal fluid concentrations of the monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (HMPG) were measured by high-performance liquid chromatography with electrochemical detection, as previously described.[10] The measurements were performed by board-certified laboratory technicians who were blinded to clinical data.

2.4. Statistical analysis

Between-group comparisons of continuous data were conducted through the Mann-Whitney U test; the χ^2-analyses were used for categorical variables. Effect size for the Mann-Whitney U test was estimated through calculation of eta-squared (η^2). Bivariate correlations were evaluated using Spearman rho. Owing to non-normal distribution, CPM data were categorized into above/below median to facilitate analyses of relationships between monoamine metabolite levels and pain inhibitory capacity. Both absolute (kPa) and relative (percentage) levels of descending pain inhibition were evaluated. Multivariable linear regression models, adjusting for age, sex and body mass index (BMI), were used to examine associations between CSF levels of monoamine mediators and clinical pain measures or neurophysiological variables. Regression analyses were also used to test associations between preoperative monoaminergic activity and long-term postoperative pain control measures, adjusting for both demographic variables and preoperative pain severity. Fulfillment of model assumptions was confirmed through visual inspection of residuals and other model features. Based on previous findings related to CSF proinflammatory mediators and QST measures of central sensitization,[8] the following 2 subgroup analyses of monoamine metabolite levels were predetermined: (1) arm PPDT < 250 kPa vs ≥ 250 kPa (<250 kPa represents a level 2 standard deviation below the mean PPDT in a healthy, non-OA population[48]), (2) temporal summation <2 vs ≥ 2 in the area of maximum pain (ie, below/above median in the current data set because no relevant a priori cutoff level was available). There were no missing clinical preoperative data and almost no missing longitudinal follow-up data (0.2%). It was not possible to determine HMPG levels in 6 patients with OA; all other monoamine metabolite data were complete. P values < 0.05 were considered to indicate statistical significance. Analyses were performed in SPSS software, version 25 (IBM Corp, Armonk, NY).

2.4.1. Sample size calculation

Sample size power calculations based on estimated interleukin 8 group differences have previously been provided.[8] For this

secondary analysis of the neuroPSI data, we confirmed that the sample size was adequate for between-group comparisons of monoamine metabolites. Using previously reported results comparing CSF 5-HIAA levels between patients with chronic pain and controls,[44] we found that detection of a significant CSF 5-HIAA difference, with a 2-sided significance level of 5% and power of 90%, produced estimates of 24 subjects in each group.

3. Results

3.1. Demographic characteristics

Demographic characteristics of the study participants are summarized in **Table 1**. There were no significant age or sex distribution differences between the OA and control groups, but patients with OA had higher BMI and lower education level. All subjects were Anglo-American.

3.2. Clinical characteristics of patients with osteoarthritis and pain-free controls

Three patients with OA were classified as ASA physical status 3; the remaining 49 were ASA 1 or 2. The most common medical diagnoses among patients with OA were hypertension (n = 25), obesity grade 1 (ie, BMI 30–35 kg/m^2, n = 12), stable ischemic heart disease (n = 5), and hypothyreosis (n = 4). Paracetamol and/or nonsteroidal anti-inflammatory drugs were commonly used by patients with OA, but opioid treatment was rare (codeine n = 6, morphine n = 4, and oxycodone n = 2). Two patients with OA were taking gabapentinoids because of pain. Only 3 of 30 controls were diagnosed with a relevant comorbidity (localized lichen ruber, unspecified joint problems, and synovial

chondromatosis of the temporomandibular joint); none of these 3 subjects were using analgesics/anti-inflammatory medications. Patients with OA experienced moderate to severe, disabling pain (**Table 1**). Anxiety and depression scores were low for both groups, with no significant differences (**Table 1**). Use of selective serotonin reuptake inhibitors (SSRIs) was more common among patients with OA (n = 4) compared with those among controls (n = 1). Two patients with OA were taking SNRIs, and 1 patient in the OA group was prescribed amitriptyline as part of multimodal pain management plans. Compared with pain-free controls, patients with OA reported poorer sleep quality during the past month (**Table 1**). Patients with OA had high mean PSQI and ISI scores, indicative of disturbed sleep continuity and poor sleep quality.

3.3. Comparison of cerebrospinal fluid levels of monoamine metabolites: patients with osteoarthritis vs pain-free controls

Levels of HMPG were higher for patients with OA compared with those for controls (medium effect size, η^2 = 0.06); there were no significant group differences regarding 5-HIAA or HVA (**Table 1**). All monoamine metabolites correlated with each other (5-HIAA–HMPG ρ = 0.407, P < 0.0005; 5-HIAA–HVA ρ = 0.697, P < 0.0001; and HMPG–HVA ρ = 0.271, P = 0.018).

Sensitivity analyses showed that subjects who were using SSRI or SNRI medications (patients with OA, n = 6; controls, n = 1) had lower levels of 5-HIAA and HMPG compared with subjects not taking these medications (n = 75) (99.0 [27.0] vs 149.0 [80.0] ng/mL, P = 0.008, and 46.0 [12.0] vs 53.0 [14.0] ng/mL, P = 0.026, respectively). Exclusion of subjects using SSRI or SNRI

Table 1
Baseline demographic and clinical characteristics and cerebrospinal fluid levels of monoamine metabolites: patients with hip osteoarthritis (n = 52) vs controls (n = 30).

Variable	Patients with osteoarthritis	Pain-free controls	P
Demographic			
Age (y)	70.4 ± 8.3	67.8 ± 6.6	0.21
Sex (male:female)	21:31	14:16	0.65
Body mass index (kg/m^2)	28.0 ± 3.7	25.3 ± 2.9	0.002
Smoking (%)	5.8	6.7	0.87
Education level (% 7–9:10–12:more than 12 y)	42.3:34.6:23.1	25.0:21.4:53.6	0.02
Clinical			
HADS anxiety (0–21)*	4.7 ± 3.8	3.7 ± 4.5	0.29
HADS depression (0–21)*	3.7 ± 3.0	2.3 ± 3.2	0.06
Sleep quality (% very good:fairly good:fairly bad:very bad)	11.5:42.3:28.8:17.3	22.2:63.0:14.8:0	0.02
ISI score (0–28)†	10.2 ± 7.0	NA	—
PSQI global score (0–21)‡	9.2 ± 5.0	NA	—
BPI pain severity (0–10)§	5.4 ± 1.3	NA	—
BPI pain interference (0–10)§	5.9 ± 1.8	NA	—
DN-4 score (0–10)‖	2.0 ± 1.5	NA	—
WOMAC OA pain score (0–20)¶	11.2 ± 3.3	NA	—
EQ-5D pain score (1–5)#	3.5 ± 0.6	NA	—
CSF monoamine metabolites			
5-HIAA (ng/mL)	138.0 (93.0)	148.0 (71.0)	0.90
HMPG (ng/mL)	55.5 (14.0)	49.5 (16.0)	0.04
HVA (ng/mL)	245.5 (141.0)	293.0 (163.0)	0.20

* The HADS is composed of 7 items related to anxiety and 7 items related to depression, each scored 0 to 3. Anxiety and depression scores 0 to 7 are considered normal, 8 to 10 borderline abnormal, and 11 to 21 abnormal.
† The ISI yields a total score of 0 to 28; 0 to 7: no clinically significant insomnia, 8 to 14: subthreshold insomnia, 15 to 21: clinical insomnia (moderate severity), and 22 to 28: clinical insomnia (severe).
‡ Higher PSQI scores are associated with worse sleep quality; scores >5 indicate sleep disturbance.
§ The BPI pain severity score is the average of 4 pain intensity scores (maximum, minimum, average, and current pain) and ranges from 0 to 10 (0 = no pain, 10 = worst imaginable pain). The BPI pain interference score is based on pain interference related to 7 different daily activities (0 = no pain interference, 10 = complete pain interference).
‖ The DN-4 consists of 10 items, which yield a score 0 to 10. Scores ≥ 4 indicate that the pain is likely to be neuropathic in origin.
¶ Five questions of the WOMAC OA pertain to pain. The pain subscore ranges from 0 to 20 (0 = no pain, 20 = maximum pain).
# Pain, scored 1 to 5 (1 = no pain, 2 = slight pain, 3 = moderate pain, 4 = severe pain, 5 = extreme pain), is 1 of the 5 dimensions of the EQ-5D.
5-HIAA, 5-hydroxyindoleacetic acid; BPI, Brief Pain Inventory; CSF, cerebrospinal fluid; DN-4, Douleur Neuropathique-4; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HMPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; WOMAC OA, Western Ontario and McMaster Universities Osteoarthritis Index.

medications resulted in even more significant differences between patients with OA and controls regarding HMPG levels (57.0 [15.0] vs 50.0 [17.0] ng/mL, P = 0.010), but did not alter the nonsignificant differences for 5-HIAA and HVA.

Compared with men, women had higher 5-HIAA concentrations (151.5 [77.0] vs 118.0 [72.0] ng/mL, P = 0.013). There were no significant associations between age, BMI, and levels of monoamine metabolites (assessed by Spearman rho and regression analysis).

3.4. Associations between cerebrospinal fluid monoamine metabolites and clinical pain measures in patients with osteoarthritis

Previous studies evaluating CSF concentrations of monoamine metabolites in populations with chronic pain and control groups have generated mixed results[2,21,23,44]; hence, although only HMPG levels differed between patients with OA and controls in this sample, we investigated associations between all 3 monoamine metabolites and pain measures.

Multivariable linear regression models, adjusting for demographic variables (age, sex, and BMI), showed that higher 5-HIAA concentrations were associated with higher pain severity, as characterized by BPI, EQ-5D, and WOMAC OA (Fig. 1 and Table 2). Homovanillic acid showed similar associations with pain scores and was also associated with levels of neuropathic pain symptoms (Table 2). Patients with OA with clear signs of neuropathic pain, ie, DN-4 score ≥4 (n = 8), had higher HVA levels compared with those with DN-4 score < 4 (n = 44) (355.5 [219.0] vs 239.5 [127.0] ng/mL, P = 0.035). Although HMPG levels were higher in patients with OA compared with those in controls, there were no significant associations between HMPG and pain severity.

3.5. Associations between cerebrospinal fluid monoamine metabolites and quantitative sensory testing measures of central sensitization in patients with osteoarthritis

Patients with signs of central sensitization according to arm PPDT (n = 32) had higher HVA levels, compared with those with PPDT above the 250 kPa threshold (n = 20) (262.0 [186.0] vs 202.0

[110.0] ng/mL, P = 0.042, Figure 2); 5-HIAA and HMPG levels did not differ.

Comparison of monoamine metabolite concentrations in subjects with absolute levels of CPM above median vs below median showed that higher 5-HIAA and HVA concentrations were associated with lower endogenous pain inhibitory capacity (Fig. 3A and B). Conversely, higher HMPG levels were linked to more effective descending pain inhibition (Fig. 3C).

Homovanillic acid levels were significantly associated with temporal summation in the area of maximum pain (ρ = 0.304, P = 0.029). There were nonsignificant tendencies for higher monoamine concentrations among subjects with high temporal summation (temporal summation ≥2 in the area of maximum pain, n = 29) compared with those with low temporal summation (n = 22) (P < 0.2 for 5-HIAA, HMPG, and HVA).

3.6. Associations between monoamine metabolites and long-term postoperative pain outcomes

Higher 5-HIAA and HVA predicted higher pain severity 3 months after surgery, adjusting for demographic factors and baseline pain scores (Table 3, Fig. 4A). 5-HIAA also predicted pain severity 6 months postoperative (Table 3, Fig. 4B). There were no significant associations between HMPG and long-term postoperative pain outcomes (Table 3).

4. Discussion

4.1. Main findings

Comparison of CSF monoamine metabolites between patients with disabling OA pain and pain-free controls showed that patients with OA had higher levels of HMPG, whereas there were no differences in 5-HIAA and HVA concentrations. Of interest, within-OA patient analyses demonstrated that higher CSF levels of serotonin and dopamine metabolites were associated with increased clinical pain, greater central sensitization, and worse long-term postoperative pain outcomes. Whereas higher 5-HIAA and HVA levels were associated with impaired endogenous pain inhibitory capacity, increased HMPG (the major noradrenaline metabolite) concentrations were linked to more effective CPM. Although absence of QST data in control participants limit our
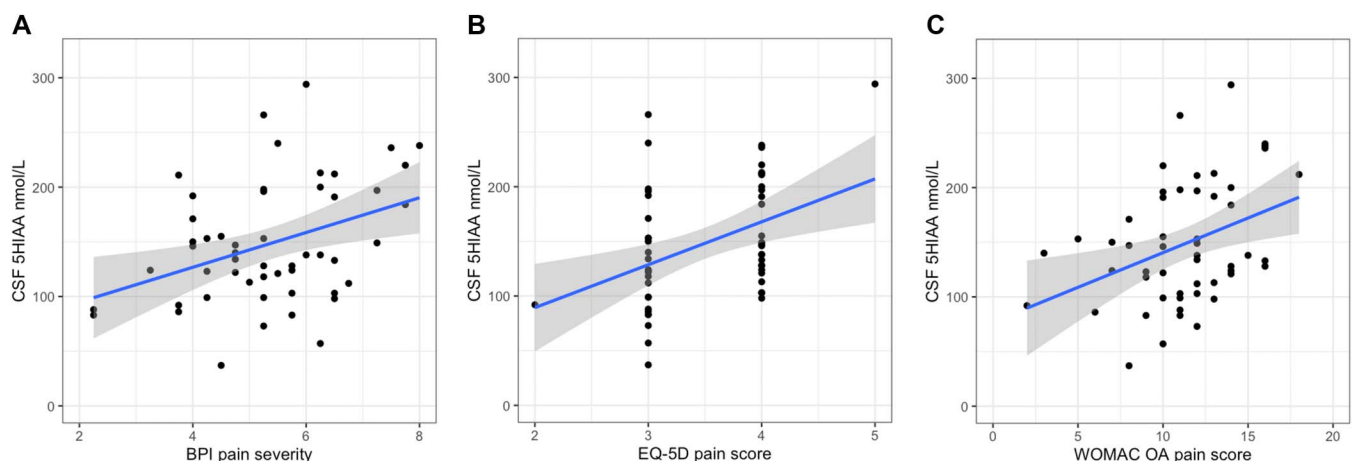
Figure 1. Associations between CSF levels of 5-HIAA and clinical pain measures: (A) BPI pain severity, (B) EQ-5D pain score, (C) WOMAC OA pain score. Regression results are summarized in Table 2. The shaded area represents the 95% confidence interval of the mean effect. 5-HIAA, 5-hydroxyindoleacetic acid; BPI, Brief Pain Inventory; CSF, cerebrospinal fluid; EQ-5D, European Quality of Life-5 Dimensions; WOMAC OA, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2

Linear regression analyses: associations between cerebrospinal fluid monoamine metabolites and preoperative pain.

Pain measure	Model 1: univariable			Model 2: adjusted for age, BMI, and sex		
	Beta (95% CI)	R^2	P	Beta (95% CI)	R^2	P
5-HIAA						
BPI pain severity	0.009 (0.003 to 0.015)	0.14	0.006	0.010 (0.004 to 0.017)	0.18	0.003
DN-4 score	0.005 (−0.002 to 0.013)	0.04	0.163	0.004 (−0.003 to 0.012)	0.23	0.233
EQ-5D pain score	0.004 (0.002 to 0.007)	0.17	0.003	0.004 (0.001 to 0.007)	0.24	0.007
WOMAC OA pain score	0.022 (0.007 to 0.038)	0.14	0.006	0.022 (0.005 to 0.039)	0.15	0.012
HVA						
BPI pain severity	0.003 (−0.0004 to 0.007)	0.06	0.079	0.003 (−0.0005 to 0.007)	0.08	0.084
DN-4 score	0.006 (0.002 to 0.010)	0.15	0.005	0.005 (0.001 to 0.009)	0.29	0.021
EQ-5D pain score	0.002 (0.0003 to 0.003)	0.11	0.019	0.001 (−0.0001 to 0.003)	0.17	0.072
WOMAC OA pain score	0.011 (0.002 to 0.019)	0.11	0.019	0.010 (0.001 to 0.019)	0.12	0.039

Betas are unstandardized.

5-HIAA, 5-hydroxyindoleacetic acid; BMI, body mass index; CI, confidence interval; DN-4, Douleur Neuropathique-4; EQ-5D, European Quality of Life-5 Dimensions; HVA, homovanillic acid; WOMAC OA, Western Ontario and McMaster Universities Osteoarthritis Index.

results, these findings support and extend previous data, indicating a relationship between CNS monoaminergic activity and pain perception.

4.2. Evaluation of cerebrospinal fluid monoamine metabolites in human pain populations

Previous studies comparing CSF concentrations of monoamine metabolites between human chronic pain populations and pain-free controls have generated inconsistent results. In one study, a mixed group of patients with chronic pain had higher CSF 5-HIAA levels than pain-free controls.[23] However, there were no CSF 5-HIAA differences between patients with acute and chronic pain. Another report also provides evidence of increased CSF 5-HIAA levels in female, but not male, patients with chronic pain compared with those in controls.[21] This study supports potential sex differences in CSF 5-HIAA levels, given that female individuals had higher levels than male individuals (full sample, n = 82). By contrast, another study (n = 40) reported that patients with chronic pain had lower CSF concentrations of noradrenaline and 5-HIAA compared with controls,[44] and patients diagnosed with idiopathic pain disorders were also found to have lower 5-HIAA levels compared with healthy controls.[2] Whereas our study found consistent associations between CSF levels of monoamine metabolites and pain intensity, as characterized by multiple instruments, previous results are equivocal.[2,21,23,44] Results from other areas of research confirm the complex relationship between concentrations of CSF monoamine metabolites and clinical outcomes; for example, meta-analyses of studies conducted in major depressive disorder populations has revealed no clear pattern of alterations in monoaminergic activity vs controls.[35]

To the best of our knowledge, only 1 previous study has concomitantly examined CSF monoamine metabolites and pain neurophysiology in humans with long-term pain, although that study included only 7 patients with chronic pain.[33] Parent et al.[33] reported no differences in CSF levels of monoamine metabolites between patients with chronic pain and controls and found no significant associations between CSF monoaminergic activity and CPM. Of interest, patients with chronic pain had lower plasma levels of noradrenaline and metadrenaline compared with controls, and there were positive correlations between these markers and CPM efficacy. Nevertheless, several methodological factors limit conclusions, such as insufficient power, heterogeneous chronic pain diagnoses, and the fact that patients with pain had only mild pain problems (mean BPI pain severity 3.0 ± 0.8). Moreover, CPM testing was conducted 3 to 5 days before CSF

sampling, which compromises interpretation of results. In our study, more efficient pain inhibitory capacity was associated with greater levels of CSF HMPG, which was significantly higher among patients with OA compared with controls, possibly reflecting adaptive noradrenergic alterations in the CNS.

4.3. Preclinical findings underlying links between monoaminergic activity and persistent pain

Preclinical models of persistent pain indicate complex alterations of monoamine signaling at supraspinal and spinal sites. Taken together, these alterations may contribute to increased central sensitization and perpetuation of pain.

Serotonin exerts receptor subtype–dependent pain modulation in the CNS. Although activation of descending serotonergic pathways originating from RVM inhibits nociceptive neurotransmission through 5-HT7 receptors,[13] the 5-HT2 and 5-HT3
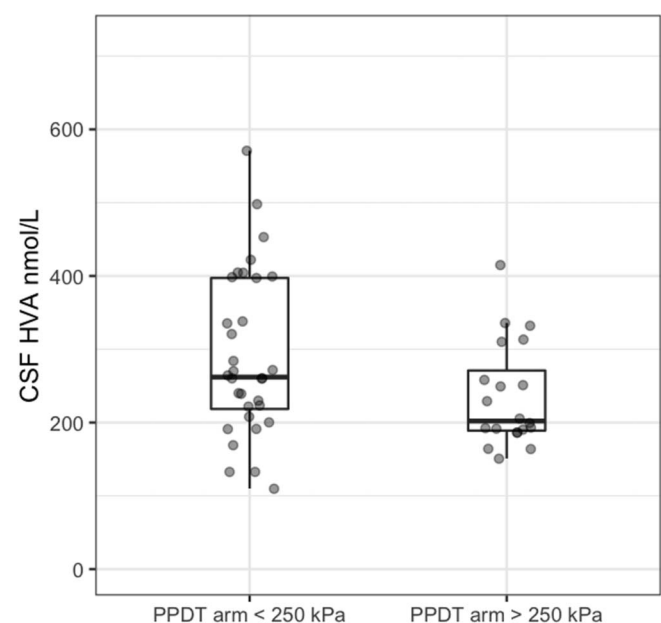
Figure 2. Comparison of cerebrospinal fluid HVA levels between patients with or without signs of possible central sensitization according to arm PPDT. Between-group comparison P value (Mann-Whitney): P = 0.042. Boxes indicate upper quartile, median, and lower quartile; whiskers indicate maximum and minimum values, respectively, excluding outliers. HVA, homovanillic acid; PPDT, pressure pain detection threshold.
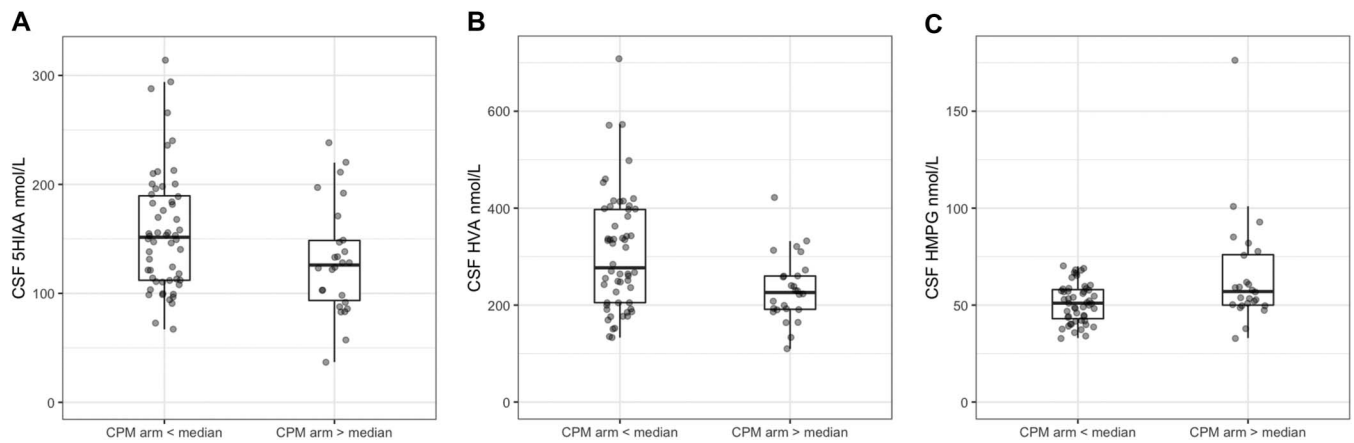
Figure 3. Analyses of cerebrospinal fluid monoamine metabolite concentrations and pain inhibitory capacity in patients with osteoarthritis: (A) 5-HIAA, (B) HVA, (C) HMPG. Between-group comparison P value (Mann-Whitney): (A) P = 0.020, (B) P = 0.022, (C) P = 0.031. Boxes indicate upper quartile, median, and lower quartile; whiskers indicate maximum and minimum values, respectively, excluding outliers. 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; HMPG, 3-methoxy-4-hydroxyphenylglycol.

receptors facilitate spinal pain transmission.[12] In inflammatory and neuropathic pain models, 5-HT2 receptors are upregulated in multiple regions of the CNS, including the dorsal root ganglion, dorsal horn, RVM, and PAG.[47,50] Antagonism of 5-HT2A receptors reduces allodynia and hyperalgesia, indicating a role for serotonin in central sensitization processes.[47] Furthermore, 5-HT3 receptors are implicated in sensitization processes during long-term pain. Five weeks after spinal cord injury, antagonism of 5-HT3 receptors decreases mechanical allodynia, and conversely, activation of these receptors augment allodynia.[32] Of interest, selective optogenetic activation of serotonergic RVM neurons seems to induce sensitization to mechanical and thermal stimuli.[15] Our findings support these preclinical results, indicating a net pronociceptive effect of serotonergic activity in which increased CSF concentrations of 5-HIAA were associated with higher pain severity and reduced endogenous pain inhibitory capacity.

Compared with serotonergic pathways, pain-related alterations of dopaminergic systems are less explored.[38] In animal models of neuropathic pain, changes in expression of dopamine receptors in the nucleus accumbens and hippocampus have been reported.[12] Moreover, stimulation of dopaminergic neurons in the PAG decreases pain behavior, and inhibition of PAG dopamine signaling attenuates opioid-induced analgesia.[20,30] Generally, stimulation of spinal D2 receptors seems to produce antinociceptive effects, whereas stimulation of D1 receptors promotes pain

transmission.[12,31] Adding to the complexity, higher local spinal concentrations of dopamine may preferentially activate the pronociceptive D1 receptor over the D2 receptor.[34] In this study, higher CSF HVA levels were linked to increased pain sensitivity and higher pain severity, indicating that dysregulated dopaminergic signaling may contribute to persistent OA pain phenotype.

Noradrenergic pathways descend from 3 pontine areas (A5, A6 [locus coeruleus], and A7) to the RVM, PAG, and the spinal cord and normally exert inhibitory influences on nociceptive transmission.[28] Notably, there are high amounts of α-adrenergic and β-adrenergic receptors in the medullary, brainstem, and brain areas involved in pain processing, eg, RVM, locus coeruleus, PAG, thalamus, and prefrontal cortex.[28,36] Of importance, α_2-adrenoceptor agonists, such as clonidine and dexmedetomidine, produce pronounced clinical analgesia through spinal and supraspinal effects, and treatments that elevate levels of noradrenaline may benefit patients who experience persistent pain.[9,19,46] Although neuroplastic changes associated with long-term pain seem to augment noradrenergic pain inhibitory signaling, involving upregulation of noradrenaline transporter and α_2-receptors and increased sensitivity of α_2-receptors, these alterations may have detrimental effects on pain-related psychopathologies.[1,12] In this study, we found that patients with OA had significantly higher CSF HMPG levels compared with pain-free controls, and higher levels of HMPG were associated with more effective CPM. Based on preclinical
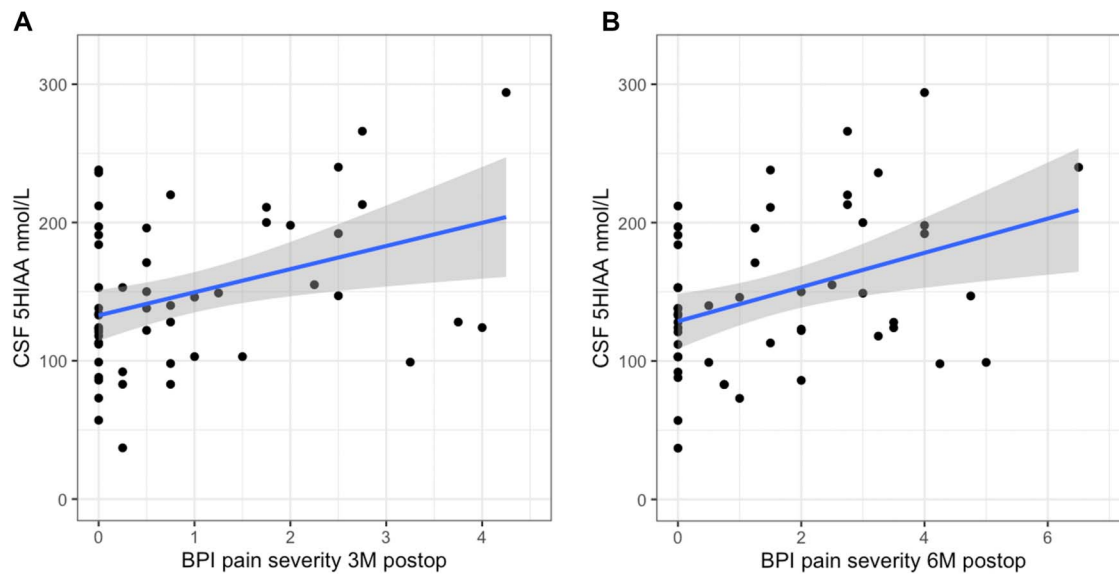
Table 3

Associations between preoperative cerebrospinal fluid monoamine metabolites and long-term postoperative pain outcomes.

Monoamine metabolite*	Pain measure	Model 1: univariable			Model 2: adjusted for age, BMI, sex, and BL pain severity		
		Beta (95% CI)	R^2	P	Beta (95% CI)	R^2	P
5-HIAA	BPI pain severity 3 mo	0.008 (0.002 to 0.014)	0.13	0.008	0.007 (0.002 to 0.013)	0.39	0.012
	BPI pain severity 6 mo	0.012 (0.004 to 0.020)	0.14	0.006	0.010 (0.001 to 0.019)	0.23	0.030
HMPG	BPI pain severity 3 mo	−0.002 (−0.019 to 0.015)	0.001	0.805	−0.005 (−0.020 to 0.010)	0.27	0.513
	BPI pain severity 6 mo	−0.001 (−0.024 to 0.022)	0.0002	0.921	−0.005 (−0.027 to 0.017)	0.16	0.660
HVA	BPI pain severity 3 mo	0.004 (0.001 to 0.008)	0.14	0.006	0.003 (0.0002 to 0.006)	0.36	0.034
	BPI pain severity 6 mo	0.004 (−0.0004 to 0.009)	0.06	0.078	0.003 (−0.002 to 0.008)	0.17	0.297

Betas are unstandardized.
* Independent predictor variable.
5-HIAA, 5-hydroxyindoleacetic acid; BL, baseline; BMI, body mass index; BPI, Brief Pain Inventory; CI, confidence interval; HMPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid.

Figure 4. Associations between preoperative levels of cerebrospinal fluid 5-HIAA and long-term pain severity after surgery: (A) 3 months postoperative, (B) 6 months postoperative. Regression results are summarized in Table 3. The shaded area represents the 95% confidence interval of the mean effect. 5-HIAA, 5-hydroxyindoleacetic acid.

evidence, alterations in noradrenergic activity could be explained by adaptive CNS changes due to long-term pain.[2,44]

4.4. Methodological considerations and future directions

Although our study provides novel data linking CNS mono-aminergic activity with pain processes in humans, several limitations should be considered. First, only patients with OA underwent neurophysiological examination; QST assessment of control participants could have further expanded knowledge about the role of monoamines in pain signaling. Second, although our sample was considerably larger than previous attempts to examine pain neurophysiology and CSF monoamines concomitantly,[33] the power and generalizability of results would have increased by inclusion of more subjects. Nevertheless, participants underwent detailed characterization, including extensive QST and CSF analyses, and our main findings were markedly consistent. Third, because CSF monoamine metabolites were assessed only preoperatively, conclusions regarding causality and temporal dynamics of monoamine systems cannot be drawn. An important strength of this study is that QST was completed approximately 1 hour before CSF sampling, which optimizes conditions for interpretation of links between pain neurophysiology and CNS monoaminergic activity. We encourage future longitudinal studies examining both alterations in pain measures and changes in CSF monoamine metabolites after joint replacement surgery.

5. Conclusions

In summary, higher CSF concentrations of serotonin and dopamine metabolites are associated with increased pain severity, central sensitization, and impaired long-term pain control after THA. These results underscore the importance of CNS monoaminergic activity in OA pain processes.

Disclosures

The authors declare no conflict of interest related to the current work.

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