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Research Article

Chronic Inflammatory Pain Alters Expression of Limbic MAPK Phosphatases

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Abstract

Brain mechanisms involved in comorbidity between chronic pain conditions and clinical depression are still largely unknown. Our previous studies demonstrated that expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) is both necessary and sufficient for the development of enhanced behavioral emotionality (i.e., depressive- like behaviors) in rodents. Here, we investigated the role of the dual specificity phosphatase (DUSP) gene family, specifically MKP-1, MKP-2 and MKP-3, in limbic brain areas involved in affective pain processing and stress responses. Male rats exposed to 21 days of peripheral inflammatory pain exhibited a robust increase in MKP-1 gene expression within the hippocampus, prefrontal cortex (PFC) and anterior cingulate cortex (ACC). Similar upregulation of hippocampal MKP-1 was also observed in female animals exposed to the same 21-day paradigm. However, the overall pattern of MKP-1 expression across various limbic areas differed in females exposed to chronic pain, as significant downregulation of MKP-1 was observed in the ACC, while no changes were detected within the PFC. Furthermore, similar limbic region-specific variances in pain-related dysregulation were also observed for MKP-2 and MKP-3. Finally, pain-induced upregulation of limbic MKP-1 was blocked by low-dose ketamine treatment (10 mg/kg) previously shown to produce rapid antidepressant effects in rodents. Overall, the results of this study suggest that chronic pain activates specific MKPs/DUSPs within limbic brain regions, which may underlie previously reported pain-related decreases in MAPK signaling. Thus, dysregulation of MKP-1 and other DUSP genes may play an important role in the development of mood disorders associated with chronic pain state.

Keywords: Pain; Depression; MKP-1; MKP-2; MKP-3; Limbic

Introduction

Approximately 45% of the U.S. population suffers from a chronic pain condition in any given year [1]; however, this prevalence will likely continue to increase over time as population ages. Chronic pain has a robust affective-motivational component evoking feelings of unpleasantness that impacts limbic brain areas involved in regulation of stress responses, eventually resulting in the development of mental health issues [2]. Indeed, clinical reports suggest that comorbid mood disorders such as anxiety and major depressive disorder (MDD) are present in up to 50% of all patients with different chronic pain conditions [3]. To date, the exact neurophysiological mechanisms linking chronic pain and mood disorders remain unclear, while standard clinical pain management practices are not directly focused on treating the affective-motivational aspects of pain. Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are commonly used to treat comorbid anxiety and depression in chronic pain patients; however, their use is often limited by lack of effectiveness and/or presence of debilitating side effects [4,5].

Recent findings suggest that the effects of chronic pain on limbic brain areas regulate mood, stress responses, cognition and emotional pain processing. Moreover, pain-evoked alterations in areas such as the hippocampus, prefrontal cortex (PFC) and anterior cingulate cortex (ACC) seem to resemble those of prolonged stress [6]. For example, we previously showed that chronic inflammatory pain produces biochemical and morphological changes in the hippocampus including decreased neurotrophic factor signaling and decreased rates of neurogenesis [7-9]. Reduced hippocampal adult neurogenesis and decreased hippocampal volume alongside behavioral alterations and cognitive deficits in learning and memory were also reported in rodents exposed to chronic neuropathic pain [10]. Moreover, recent studies also found increased expression of MKP-1 within the ACC in a neuropathic pain model [11]. MKP-1 is a dual specificity phosphatase (DUSP) that deactivates components of the mitogen-activated protein kinase (MAPK) cascade through direct dephosphorylation of its main substrates including extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 MAP kinases [12]. Stress-evoked attenuation of limbic MAPK activity, as well as upregulation following an antidepressant treatment, have been well-documented in numerous preclinical studies [13-15].

Our previous post-mortem study of depressed human brains found robust increases in MKP-1 mRNA within the hippocampal subregions CA1 and dentate gyrus [16]. Further characterization of its role in stress mechanisms showed that hippocampal MKP-1 is both sufficient and necessary for the development of increased behavioral emotionality in rodent models [16]. Besides MKP-1, other members of the MKP/DUSP family were also implicated in limbic stress-processing mechanisms and depression pathophysiology [17,18]. For example, MKP-2 (i.e., DUSP-4) was found upregulated within the hippocampus and PFC in post-mortem brains of depressed suicide subjects [19]. Furthermore, recent studies investigating sex-specific transcriptional differences and potential impact on stress-susceptibility identified MKP-3 (i.e., DUSP-6) as the female-specific hub gene in the PFC with proposed key roles in regulation of MAPK signaling, neuronal excitability and transcriptional remodeling that arises in depressed female brains [20].

Here, we further characterized pain-evoked changes in expression of MKP-1 and the related DUSP genes, MKP-2 and MKP-3, within different limbic brain regions commonly associated with regulation of stress responses and development of depression. Specifically, we performed a series of experiments to address the effects of temporal factors and sex variables on the limbic regulation of MKP/DUSP genes in pain state.

Experimental Procedures

Animals

Young adult male and female Sprague-Dawley rats (Charles River, Wilmington, MA) were pair-housed under a 12 h light/dark cycle with a constant temperature (25°C) and humidity with ad libitum access to food and water. All animals were age and weight (150-300 g) matched at the beginning of the experiments; rats in the pain groups were housed in separate rooms from the control groups. The maintenance of animal colonies and all experimental treatments were in strict agreement with the National Institutes of Health Guide for Care and Use of Laboratory Animals; all animal research protocols used in these experiments were approved by the Des Moines University Animal Care and Use Committee.

Inflammatory Pain Model

Rats were administered a subcutaneous injection of Complete Freund's Adjuvant (CFA; 50 µL per injection; Sigma Chemical Co., St. Louis, MO), a suspension of heat-killed Mycobacterium tuberculosis (strain H37Ra, 1 mg/mL), into the plantar surface of the left hind paw to induce a local, peripheral inflammatory pain response. Animals in the control group received a sham needle injection. To model a chronic inflammatory pain state, both male (n=8; Figure 1A) and female (n=10; Figure 3A) rats were administered CFA throughout the 21-day experimental paradigm (i.e., injections on days 0, 7, and 14) as previously described in our laboratory [9]. Acute inflammatory pain model consisted of administering a single CFA injection to male rats at the beginning of a 24 h experimental period (n=6; Figure 2A). To evaluate the effects of ketamine treatment, male rats we divided into one of the following experimental groups (Figure 4A): 1) control (saline/vehicle injection on day 20), 2) control + ketamine (10 mg/kg ketamine, single intraperitoneal injection on day 20), 3) CFA (21-day CFA paradigm as described in Figure 1; saline/vehicle injection on day 20), and 4) CFA + ketamine (10 mg/kg ketamine, single intraperitoneal injection on day 20 of CFA paradigm). At the end of each study, animals were sacrificed followed by collection of brains and spinal cords. Brains were immediately dissected; hippocampal, PFC and ACC tissues were snap-frozen and stored at -80°C for biochemical analysis.

Quantitative Real-Time Polymerase Chain Reaction (qPCR)

Total RNA was extracted from the contralateral brain regions (i.e., in reference to left-sided CFA injections) using either the RNeasy® Lipid Tissue Mini Kit (Males; QIAGEN, Hilden, Germany) or the PARISTM Kit (Females; Ambion/Thermo Fisher Scientific; Waltham, MA) according to the manufacturer's

instructions. DNase treatment was subsequently performed using either the RNase-Free DNase Set (QIAGEN, Hilden, Germany) or TurboDNase (Ambion; Waltham, MA). RNA concentrations were determined using a NanoDrop 8000 UV-Vis Spectrophotometer (Thermo Fisher Scientific, Waltham, MA). The corresponding cDNA was made from 1000ng of total RNA in 20 µL reactions using High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, MA). Expression of target genes was analyzed using a hot-start SYBR Green method in a Bio-Rad CFX96 Connect Real-Time instrument (Bio-Rad, Hercules, CA) set for 40 cycles as follows: 10 s at 94°C (denaturation), 30 s at 60°C (annealing), and 30 s at 72°C (elongation). qPCR reaction mixtures (16 µL total volume) contained 1 µL of cDNA, 1 µL of 5 pmol/µL primer mix, 6 µL of nuclease-free water, and 8 µL of SYBR Green Supermix (Bio-Rad). mRNA fold changes were calculated using the ΔΔCt method based on normalization to the expression of a house-keeping genes (GAPDH, HMBS or β-Actin) as previously described [21]. Primers were designed using Primer3web 4.1.0 online software (http://primer3.ut.ee) as shown in Table 1.

Gene	5' Primer Sequence	3' Primer Sequence
GAPDH	ggcagcccagaacatcatccctg	ggtaggaacacggaaggccatgc
HMBS	ggaaagaccctggaaaccttgcc	gcactgaactcctgcagctcatc
b-*Actin*	gacctgacagactacctcatgaag	cacagcttctctttaatgtcacgc
MKP-1	ctcgacgccttgggtatcactgc	gtcaatcgcctcgttgaaccagg
MKP-2	tctactcggctgtcatcgtctac	acctctcatagccacctttaagc
MKP-3	cgactcttcctcggacattgag	actcttccaacacgtccaagttag

Table 1: List of specific primer sequences targeting housekeeping genes (GAPDH, HMBS, β-Actin) and DUSP genes of interest (MKP-1, MKP-2, MKP-3) in qPCR analysis.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 10 software (GraphPad Software, Inc.; La Jolla, CA). For comparisons between two experimental groups, Student's t-test was performed. In experiments with three or more experimental groups differing by a single factor, 1-way analysis of variance (ANOVA) was performed followed by Tukey's post hoc comparison between each experimental group and the control group. In experiments with four experimental groups differing by two factors, two-way ANOVA was performed. Individual values that were two standard deviations above/below the mean were considered as outliers and were excluded from the final statistical analyses. Statistical significance was considered as $p \leq 0.05$.

Results

To determine the effects of chronic pain state on the limbic regulation of MKP-1, MKP-2, and MKP-3 genes, we performed a series of experiments in rats with specific emphasis to assess the influence of temporal and sex factors. Gene expression was measured within the male and female hippocampus, PFC and ACC – brain structures thought to contribute to affective-motivational pain-processing. Temporal effects were determined by exposing rats to either acute (24 h) or chronic (21 days) peripheral CFA administration. Finally, the effects of rapid antidepressant treatment with ketamine on the limbic expression of the target genes was determined in the chronic CFA model.

Chronic pain alters limbic MKP-1 and MKP-3 levels in male brains. Male rats subjected to 21 days of CFA injections exhibited a significant upregulation of MKP-1 gene in the hippocampus contralateral to pain stimulus as compared to controls (1.47-fold increase; p=0.0038; Figure 1B). These results are consistent with our previous reports showing increases in hippocampal MKP-1 in rats exposed to chronic stress. Moreover, chronic CFA administration also evoked robust increase in MKP-1 mRNA levels within the contralateral PFC (1.80-fold; p=0.0076; Figure 1B) and ACC (1.65-fold increase, p=0.010; Figure 1B), additional brain regions thought to be a part of the neurocircuitry responsible for cognitive and affective pain processing. These findings are in line with previous reports showing similar increase in MKP-1 activity in the ACC of rodents exposed to chronic neuropathic pain (Barthas et al., 2017). Interestingly, MKP-1 expression was not changed within the contralateral dorsal horn (Figure 1B), a key spinal structure involved in afferent neurotransmission of nociceptive signals from the peripheral sensory nerves to the supraspinal brain centers. Surprisingly, expression of MKP-2 gene was not significantly affected by chronic pain state in any of the studied limbic regions or the dorsal horn of the spinal cord (Figure 1C), although this member of the DUSP family was previously implicated in depression pathophysiology [19]. Finally, MKP- 3 mRNA levels were significantly elevated in the PFC (1.34-fold increase; p=0.0018; Figure 1D) and ACC (1.37-fold; p=0.004, Figure 1D) of male brains; however, no changes were observed in the hippocampus or the spinal cord.

Chronic pain alters limbic MKP-1, MKP-2 and MKP-3 levels in female brains. Female rats exposed to 21 days of CFA exhibited significant upregulation of the hippocampal MKP-1 (1.39-fold increase, p=0.0071; Figure 2B), alike to our findings in male animals subjected to the same pain paradigm. However, contrary to the males, female brains showed a robust downregulation of the MKP-1 gene in the ACC (0.60-fold decrease, p=0.0261; Figure 2B), while no changes were detected in the PFC and spinal cord. Additionally, female PFC also exhibited a significant downregulation of both MKP-2 (0.56-fold decrease; p=0.0148;

Figure 2C) and MKP-3 (0.74-fold decrease; p=0.0091; Figure 2D) genes. Chronic pain-evoked decreased expression of MKP-3 within the PFC resembles recently reported decreases in MKP-3 activity within human female MDD brains [20].

Hippocampal MKP-1 and MKP-2 levels are altered by acute pain. This experiment was performed to delineate the temporal aspects of DUSP gene expression in the inflammatory pain state. Here, we determined the expression of MKP/DUSP genes within the contralateral hippocampus and PFC of male rats exposed to CFA for 24 h. Similarly to chronic pain, acute exposure to CFA yielded significant upregulation of the hippocampal MKP-1 gene (1.42-fold increase; p=0.0292; Figure 3B); however, no changes in MKP-1 activity were observed in the PFC. Conversely, acute pain evoked significant downregulation of the hippocampal MKP-2 gene (0.81-fold decrease; p=0.0058; Figure 3C), while no changes were observed in the PFC. Furthermore, acute pain had no effect on the expression of MKP-3 mRNA in either the hippocampus or PFC (Figure 3D).

Ketamine antidepressant treatment mitigates chronic pain-derived alterations in hippocampal MKP-1 activity. The final experiment in this study was conducted to determine whether antidepressant properties of ketamine are sufficient to influence limbic MKP/DUSP gene expression in male rats exposed to the 21-day CFA paradigm (Figure 4A). Consistent with previous experiments, 2-way ANOVA showed that the main effect of pain is significant in the hippocampus (F1,20=5.592; p=0.0283; Figure 4B) as CFA group exhibited a significant upregulation of MKP-1 when compared to the control group (p=0.0224; Figure 4B). However, there was also a significant interaction between the effects of pain and drug treatment (F1, 20=4.551; p=0.0455; Figure 4B) as single ketamine administration (10 mg/kg) reversed CFA-induced increases in hippocampal MKP-1 expression (i.e., MKP-1 mRNA levels were normalized to baseline). Furthermore, 2-way ANOVA also revealed that the main effect of pain is significant in the PFC (F1,20=5.418; p=0.0305]; however, the interaction between pain and ketamine treatment was nonsignificant (F1,20=3.313; p=0.084) even though MKP-1 gene expression returned to control-like levels following ketamine administration as observed in the hippocampus. Lastly, 2-way ANOVA revealed no effect of ketamine on chronic pain/CFA-evoked dysregulation of MKP-2 and MKP-3 genes in either the hippocampus or PFC (data not shown).

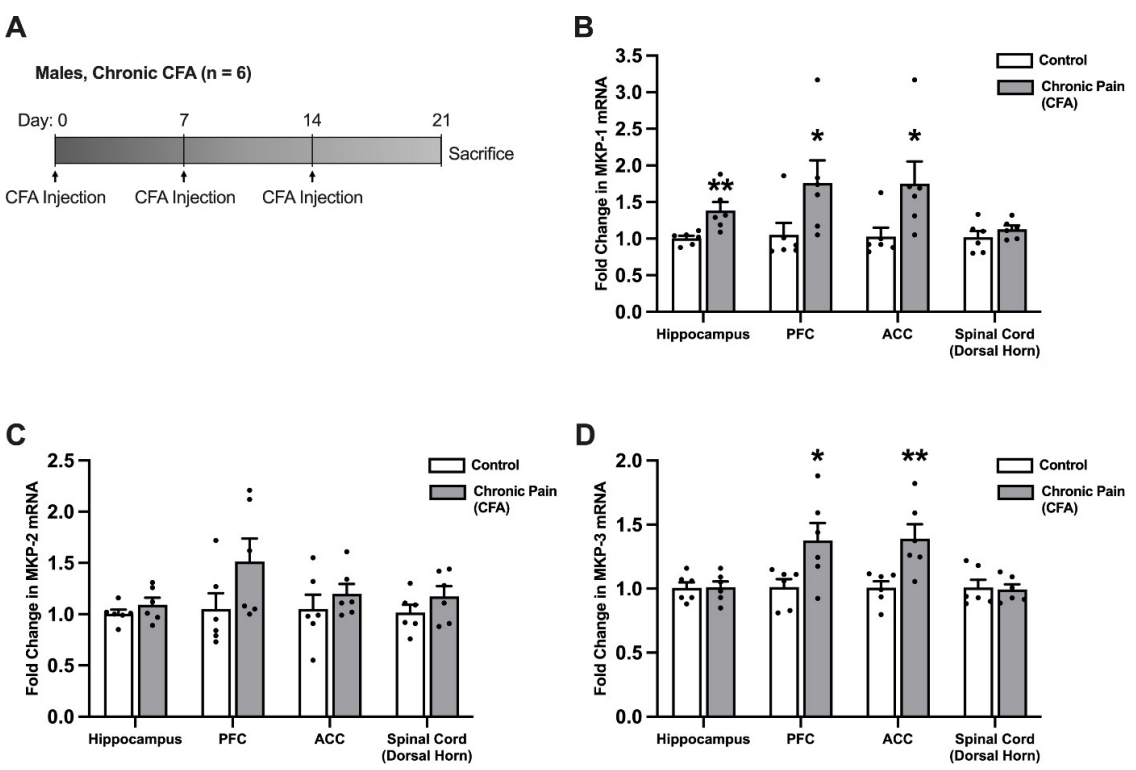

Figure 1: Expression of MKP/DUSP genes is altered by chronic pain in specific limbic regions of male rat brains. Following exposure to 21 days of peripheral inflammatory pain (**A**), mRNA expression levels of MKP-1 (**B**), MKP-2 (**C**)**,** and MKP-3 (**D**) were analyzed using qPCR in the contralateral hippocampus, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and ipsilateral spinal dorsal horn of male rats. Fold changes are expressed as mean ± SEM. (n = 6). *p<0.05, **p<0.01 compared to naïve controls, Student's t-test.

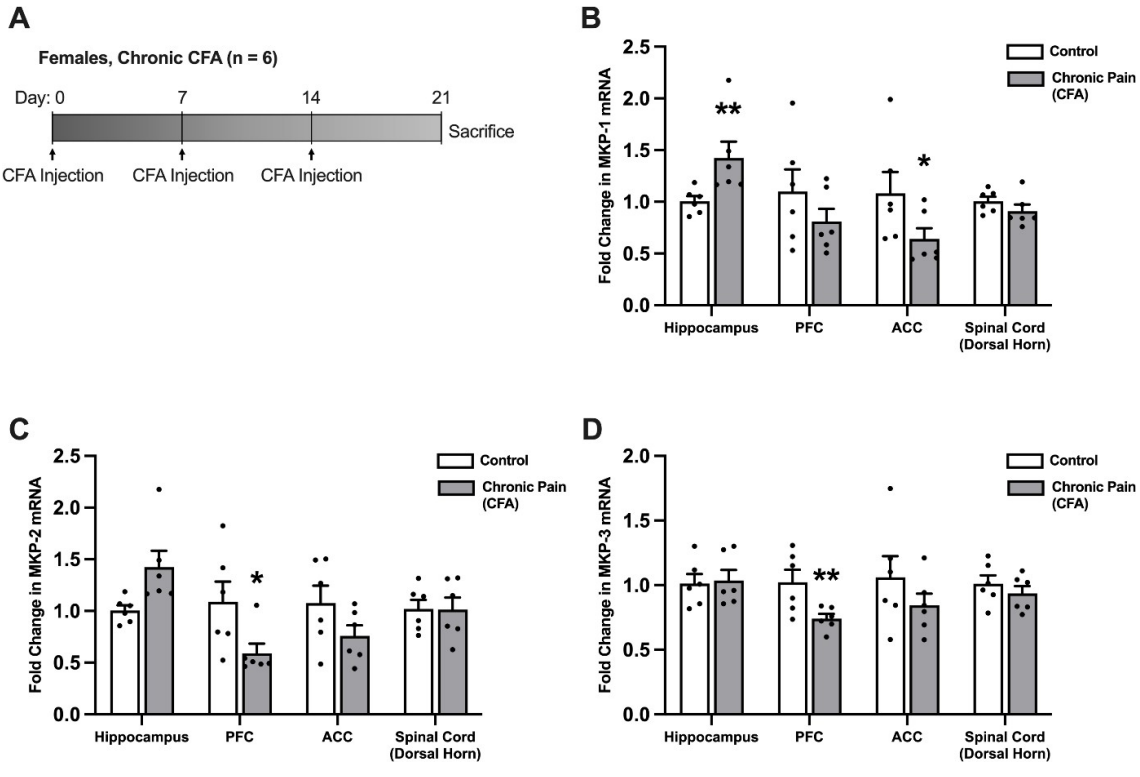

Figure 2: Expression of MKP/DUSP genes is altered by chronic pain in specific limbic regions of female rat brains. Following exposure to 21 days of peripheral inflammatory pain (**A**), mRNA expression levels of MKP-1 (**B**), MKP-2 (**C**)**,** and MKP-3 (**D**) were analyzed using qPCR in the contralateral hippocampus, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and ipsilateral spinal dorsal horn of female rats. Fold changes are expressed as mean ± SEM. (n = 6). *p<0.05, **p<0.01 compared to naïve controls, Student's t-test.

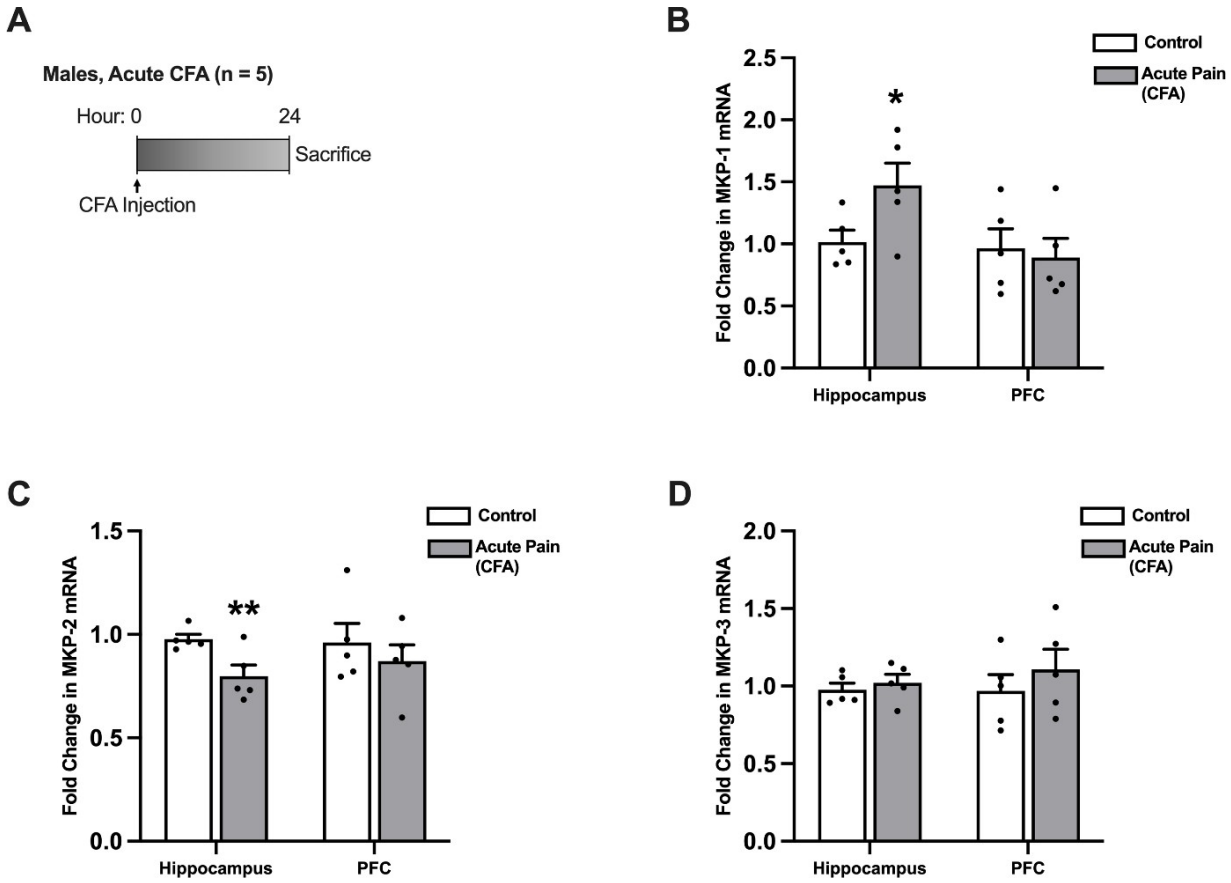

Figure 3: Effects of acute pain exposure on expression of limbic MKP/DUSP genes in male rat brains. Following a 24 h exposure to peripheral inflammatory pain (**A**), mRNA expression levels of MKP-1 (**B**), MKP-2 (**C**)**,** and MKP-3 (**D**) mRNA were analyzed using qPCR in the contralateral hippocampus and prefrontal cortex (PFC) of male rats. Fold changes are expressed as mean ± SEM. (n = 5). *p<0.05, **p<0.01 compared to naïve controls, Student's t-test.

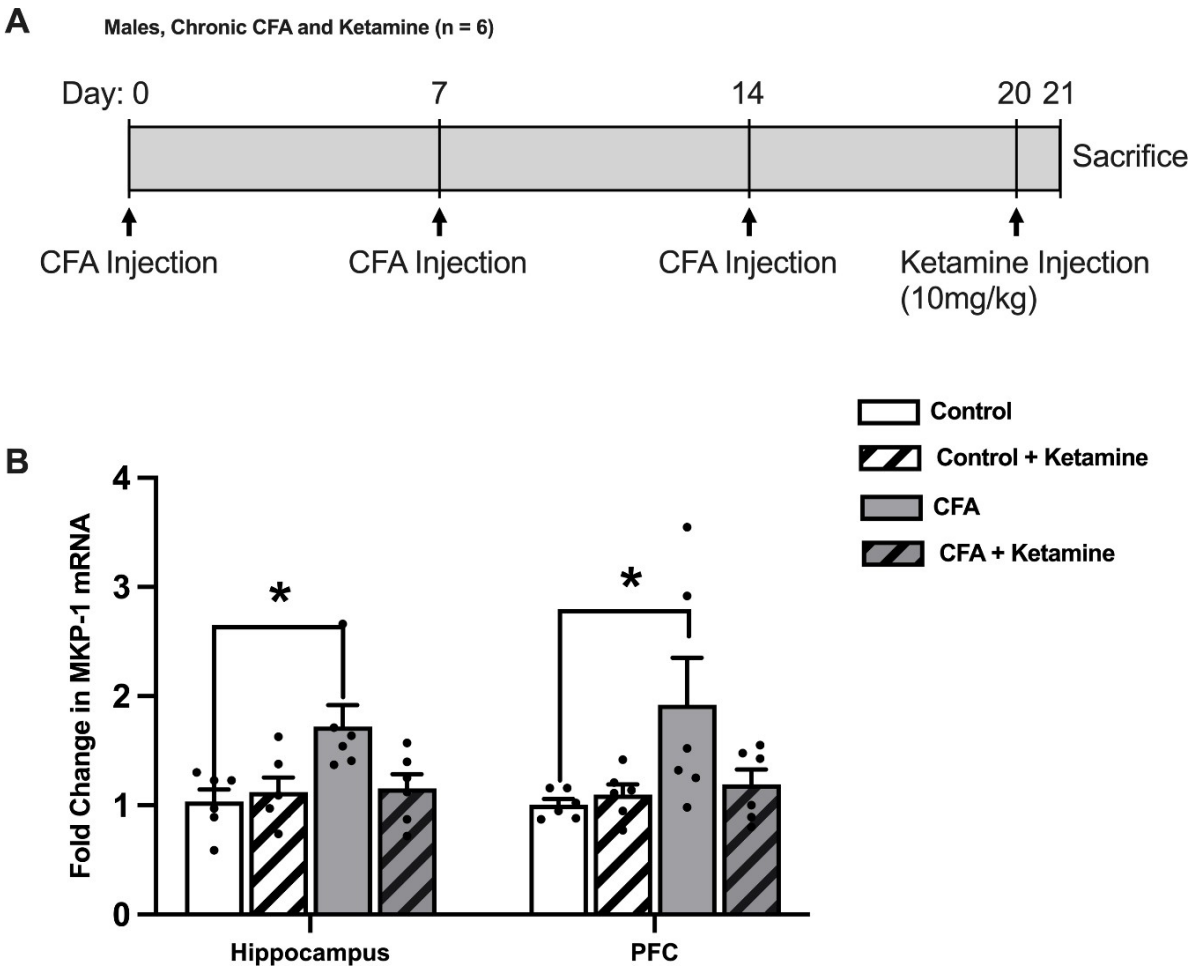

Figure 4: Rapid antidepressant effects of ketamine are sufficient to influence limbic MKP/DUSP gene expression in male rats exposed to chronic pain. A) Single ketamine injection (10 mg/kg) was administered on day 20 of CFA paradigm (i.e., 24 h before sacrifice). Levels of MKP-1 mRNA were analyzed using qPCR in the contralateral hippocampus and prefrontal cortex (PFC) of male rats exposed to 21 days of inflammatory pain with or without ketamine treatment (**B**). Fold changes are expressed as mean ± SEM. (n = 6). *p<0.05, compared to controls 1-way ANOVA with Tukey's multiple comparisons test.

Discussion

Biochemical and neural brain mechanisms linking affective-motivational component of pain and development of comorbid depression are still not well understood. Recent studies have linked dysregulation of individual MKP/DUSP genes to damaging effects of chronic stress on specific limbic brain regions and ensuing development of depression. For example, prolonged activation of hippocampal MKP-1, as seen in brains of stressed rodents and depressed human subjects [16], may underlie molecular changes such as diminished MAPK signaling and altered neuronal morphology/ atrophy. However, the potential role of MKP-1 and similar phosphatases in limbic pain processing and brain mechanisms linking chronic pain and depression are yet to be determined. Thus, in this study, we show that prolonged exposure to peripheral inflammatory pain produces robust MKP-1 upregulation in the hippocampus, PFC and ACC of both male and female animals. This is consistent with observations of increased MKP-1 activity in the ACC of rodents exposed to chronic neuropathic pain where viral knockdown of MKP-1 prevented development of depressive-like behaviors [11]. Interestingly, in this study we also show that pain-evoked effects on limbic MKP-1 activity are sensitive to rapid antidepressant treatment, as MKP-1 upregulation was blocked by low-dose ketamine treatment within both the hippocampus and PFC. Although the exact mechanisms of

ketamine's antidepressant effects have not been fully delineated, it is feasible that stabilization of MKP-1 activity and downstream normalization of MAPK signaling are contributing factors. Our results also indicate that the hippocampal upregulation of MKP-1 occurs during the acute stages of pain (i.e., within the first 24 h), while dysregulation of MKP-1 in the PFC likely occurs as pain transitions from acute to chronic. However, having only two time points is a limitation of the current experimental design. Future studies could investigate a more thorough time-course and different regulatory mechanisms involved in MKP-1's role in affective pain processing within different limbic areas, such as responsiveness to corticosterone receptor activation, epigenetic modifications as well as corresponding changes in abundance and phosphorylation of MKP-1 protein.

In addition to MKP-1, we also demonstrate that chronic pain produces robust upregulation of MKP-3 within the PFC and ACC of male animals. MKP-3 was previously implicated in therapeutic effects of antidepressants and psychostimulants as a key modulator of protein kinase C (PKC)-dependent internalization of norepinephrine transporter (NET) and dopamine transporter (DAT) [22,23]. Unlike MKP-1 and MKP-3, our results suggest that chronic pain may not produce as robust effects on regulation of limbic MKP- 2 activity (i.e., nonsignificant increases in MKP-2 mRNA were observed only in the male PFC). These finding are not aligned with the increased activity of MKP-2 previously observed in the hippocampus and PFC of depressed human brains [19]. Interestingly, a significant downregulation in hippocampal MKP-2 was observed at the acute pain stage (24 h post CFA injection), suggesting that MKP-2 may be involved in initial limbic pain processing; however, additional temporal and region-specific studies are needed to fully evaluate this idea. Altogether, the results of the current study strengthen the notion that altered activity of different genes in the MKP/DUSP family may play a role in the development of mood disorders associated with chronic pain.

In recent years, an increased significance has been placed on the potential effects of sex factors onto different neurological and psychological aspects of both chronic pain and major depression. Indeed, many recent studies demonstrated significant sex differences in the experience of these illnesses ranging from the level of symptomology to gene expression profiles [20,24]. In our study, the overall expression patterns of MKP/DUSP genes in the female hippocampus resembled male rats, suggesting that hippocampal MKPs/DUSPs are potentially not significant contributors to sex variations. In contrast, differential patterns of MKPs/DUSPs expression were observed in the female PFC where chronic pain evoked downregulation of all three genes. To our knowledge, altered expression of MKP-1 and MKP-2 in the PFC under either chronic pain or stress conditions has not been previously reported, while pain-evoked downregulation of MKP-3 in the PFC of female rats is consistent with recently observed decreases in MKP-3 activity in the PFC of stressed female brains [20]. Indeed, the study by Nestler's group reported a significant downregulation of MKP-3 gene in the ventromedial prefrontal cortex (vmPFC) of depressed human female subjects as well as female rodents exposed to chronic stress [20]. In fact, stress-evoked downregulation of MKP-3 in the PFC of females, but not males, was shown to stimulate behavioral stress-susceptibility. Subsequently, MKP-3 was identified as a female-specific hub gene that is linked to transcriptional remodeling and accompanying changes in intracellular signaling and neuronal activity of depressed female brains [20]. Overall, our results are consistent with the idea that the PFC is one of key limbic regions involved in sex differences under stress-like conditions such as chronic pain. However, additional animal studies (e.g., viral-vector gene transfer approaches) are needed to determine if MKP-3 plays a comparable role of a hub gene directly linked to development of comorbid depression in females suffering from chronic pain.

In sum, the main findings of this study further support the idea that aberrant MKP- 1 activity in the hippocampus is an important factor contributing to the development of enhanced behavioral emotionality associated with different prolonged stress conditions including chronic pain. Altered levels and activity of other members of the MKP/DUSP family of phosphatases, especially MKP-3, may additionally underlie damaging effects of chronic pain on the limbic brain areas and potentially contribute to depression susceptibility in females. Finally, further preclinical studies are needed to expand our understanding of MKP/DUSP phosphatases and their role in stress pathophysiology, which may ultimately yield novel targets for improved treatment of not only MDD, but also mental health comorbidities associated with other neurological and systemic illnesses such as chronic pain.

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Author Contributions

Dakota Nerland: Conceptualization, Investigation, Methodology, Data Curation, Validation, Formal Analysis, Writing – Original Draft. **Allison Ash:** Investigation, Data Curation, Formal Analysis, Review and Editing. **Adam Garman:** Methodology, Data Curation, Formal Analysis, Review and Editing. **Jeffery Foltz:** Formal Analysis, Review and Editing. **Gabriel Berenbeim:** Investigation. **Benjamin Wilke:** Investigation. **Lori Winter:** Investigation, Supervision. **Daniel Christian:** Review and Editing, Resources. **Vanja Duric:** Conceptualization, Investigation, Methodology, Data Curation, Validation, Formal Analysis, Writing – Original Draft, Review and Editing, Supervision, Project Administration, Funding Acquisition, Resources.

Declaration of Interest: None.

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