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Chronic Exposure to Morphine Leads to a Reduced Affective Pain Response in the Presence of Hyperalgesia in an Animal Model of Empathy

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Original Article

Abstract

Background: Empathy is the capability to represent the mental and emotional states of other subjects. Previous studies have demonstrated a possible correlation between morphine addiction and altered empathy response in morphine-addicted subjects. This study was performed to evaluate the effect of chronic morphine exposure as an animal model of morphine addiction on empathic changes in affective and sensory pain.

Methods: Adult male Wistar rats (3 months old) were used for the current study. Animals were grouped in cages of two (n = 8 for each group) and one animal was selected as the pain observer group. Pain observer animals received either saline or morphine (10 mg/kg, twice daily for 8 days). At ninth day, formalin [50 µg, 5%, subcutaneous **(**SC)] was injected into the hindpaw of the cagemate and placed inside the cage. Elevated plus maze (EPM) and open field test (OFT) were recruited to evaluate anxiety; hot plate and tail flick tests were used to assay sensory pain. Conditioned place aversion (CPA) was also measured as indicator of affective pain component.

Findings: Chronic morphine exposure led to a reduced level of anxiety in EPM and OFT assays. An opioid-induced hyperalgesia was observed in the sensory pain assays, while there was a reduced affective pain in the CPA paradigm in morphine-treated animals.

Conclusion: It might be plausible that chronic morphine exposure might alter empathy for pain through affective and not sensory pain pathways.

Keyword: Empathy; Pain perception; Morphine dependence; Rats

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Introduction

Addiction to opioids is a major health issue globally and has many negative consequences for the subjects involved.[1] It has been estimated that about 20% of the general population use opioids throughout their lifetime and opioids pandemic has become a disaster for many developed countries.[2] Empathy is the capability to mentally represent the feelings and emotional states of other people and studies in the last decades have demonstrated that many species including primates and rats possess empathy-like behaviors.[3,4]

It has been shown that observing others in pain and sensory pain share the same neurological mechanisms involving opioid receptors[5,6] and oxytocin is highly involved in empathy for pain.[7] For instance, placebo analgesia, which recruits opioid system to modulate pain, has been demonstrated to alter empathy for pain in human subjects and thus, a significant role has been designated to opioids in the empathy process.[8,9]

Chronic use of morphine alters synaptic transmission and neural function at different levels and leads to altered cognition and emotional regulation.[10] Effects of addiction to morphine on cognition and mentality have been demonstrated,[11,12] but few studies have evaluated the effects of chronic use of morphine on emotional empathic pain.[13,14] Verdejo-Garcia has demonstrated impaired social cognition, emotional recognition, and empathy in cocaine addicts.[12] Nazeri et al. have demonstrated that opioid system altered empathy-like behaviors in rats and acute morphine administration of opioids led to a decreased empathy-like response in the pain observing animals, reversed by administration of opioid antagonist naloxone.[8] Furthermore, affective component of empathic pain is altered by observing a conspecific in pain[15] and chronic morphine administration.[16]

Considering the role of opioidergic system in the modulation of empathic pain, this study was conducted to assess the effects of chronic morphine exposure on empathic behaviors in rats and altered affective pain component in animal model of empathy. Findings of this study might provide a platform for further research on the adverse social consequences of addiction to morphine and also the mechanisms of empathy in animals.

Methods

In the experimental study, adult male Wistar rats were obtained from Kerman Neuroscience Research Center, Kerman, Iran, and used in the current study (n = 8 for each group, weighing 250-280 g). After obtaining ethical confirmation from Ethics Committee of Kerman University of Medical Sciences, Kerman, and Ethics Committee of AJA University of Medical Sciences, Tehran, Iran, the study was initiated. Effort was made to minimize unnecessary harm (AJAMU-98/4). Rats were kept in cages of two for a one-month period. Animals had free access to food and water and were held in standard laboratory conditions (temperature: 23-25 ˚C and 12/12 hours dark/light).

Animals were kept in cages of two; one animal was designated as the pain observer and the other one underwent injection of formalin into the hindpaw. A valid animal model for addiction to morphine was used in the current study.[17] Observer animals either received saline or morphine [10 mg/kg, intraperitoneal **(**IP)] for 8 consecutive days and after 8 days, the experiments to evaluate the effects of empathy on locomotion, anxiety-like behaviors, and affective pain component were commenced.

Empathy for pain was evaluated using a method previously published.[8,15] Cagemates designated as pain sufferers were injected with formalin [50 µl, 5% subcutaneous (SC), Dana Teb, Iran] into the skin of hindpaw and then the animal was placed in the cage besides the pain observer rat[15] that has already received morphine or saline for 8 days. Anxiety and pain assays were conducted on the observer rats to study the effects of chronic exposure to morphine on empathic behaviors. The following assays were performed on each animal.

Open field test (OFT): Animals were placed in the middle of the open field and their behaviors were tracked with EthoVision software (version 7.1, Noldus Information Technology, Netherlands) for a five-minute period. This apparatus was a field made of black wood [56 × 56 × 20 (height) cm]. Its floor was divided into 16 squares, delineating central and peripheral squares. These parameters were evaluated for each animal: total distance moved (TDM), time spent in center, and the number of rearing. After each trial, animals were removed from the chamber and it was cleaned with a dry cotton.[18]

Elevated plus maze (EPM): The apparatus was made of two open arms and two close arms (50 × 50 × 50 cm) at 50cm height from the ground.

Each animal was put in the center of the maze and the following parameters were recorded using a digital camera above the apparatus: number of entrance into the open and close arms and time spent in each arm.

Hot plate: A hot plate device (LE710, LSI LETICA, Spain) with a 19cm diameter plate and 30cm height plexiglass device was used. Temperature was adjusted to 52.0 ± 0.5 ˚C and reaction time was measured in each animal as the time spent between the onset of the test and observation of hindpaw licking or jumping (threshold to avoid tissue damage: 45 s).[15]

Tail flick: This test assays response to acute thermal stimulus at the spinal level. The animal was restrained in a restrainer with their tales hanging freely. The lower 5cm of the tail was marked and put under the burning confocal light emitted to the skin of the tail. Reaction time was measured from the onset of emitting to tail withdrawal as a reflex.[19]

Conditioned place aversion (CPA) for pain: A separate group of saline or morphine-treated animals was used for this assay to avoid possible impact of previous behavioral assays. The CPA apparatus consisted of 3 compartments (45 × 45 cm each). Partitions were marked either with vertical or horizontal lines or blank walls. In the preconditioning day, animals were placed in the neutral section and they could freely explore each three sections. Time spent in the compartments was recorded, and in case of no bias to a specific compartment (time spent in 1 compartment more than 60% of the total time), the assay continued. Preconditioning duration was 20 minutes. On the conditioning days (days 2-5), animals were injected with formalin solution (50 µl, 2%, SC) into either hindpaw in a specific compartment or saline (50 µl) in the other section so that each rat received formalin for 2 days matched with one section and was allowed to explore the environment for a total of 50 minutes. On the post-conditioning day (day 6), animals were again put in the blank wall portion and were free to explore the apparatus compartments. Time spent in each section was recorded for 20 minutes. The following was used to calculate CPA score:

CPA score = (time spent in the formalin-matched section in day 6) – (the time spent in the formalin-matched section in day 1).[15]

SPSS software (version 16, SPSS Inc., Chicago, IL, USA) was used to analyze the obtained data. Analysis of variance (ANOVA) followed by Tukey's post-hoc were used to compare data among groups. A P-value less than 0.05 was considered as significant. Data were presented as mean ± standard error of the mean (SEM).

Results

OFT: TDM and number of rearing were not significantly different among study groups ($P > 0.05$). Time spent in center was significantly reduced in the saline group as compared to naive and morphine groups ($P < 0.05$, ANOVA followed by Tukey's test). No significant difference was observed in the time spent in periphery among study groups ($P > 0.05$, data not shown) (Figure 1, A-C).

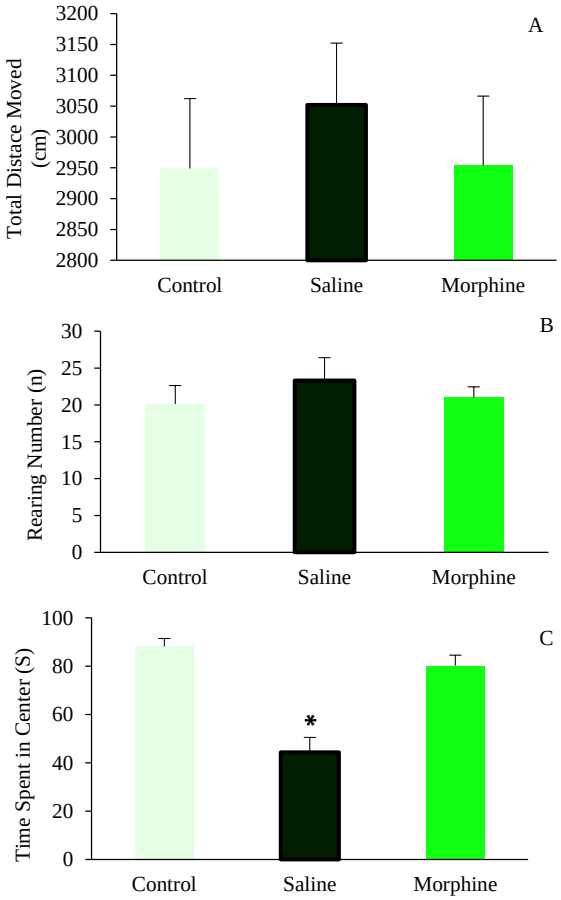

Figure 1. A) Total distance moved (TDM) was not significantly different among study groups; B) time spent in center was significantly decreased in saline-treated group. Morphine dependence reversed this effect of empathy; C) no significant difference was observed in number of rearing in the animals.
*P < 0.05 in comparison to naive rats

EPM: Duration spent and entrance frequency into the open arms were significantly diminished in the saline-treated observer rats in comparison to naive and morphine-treated animals ($P < 0.05$, ANOVA followed by Tukey's test) (Figure 2, A and B).

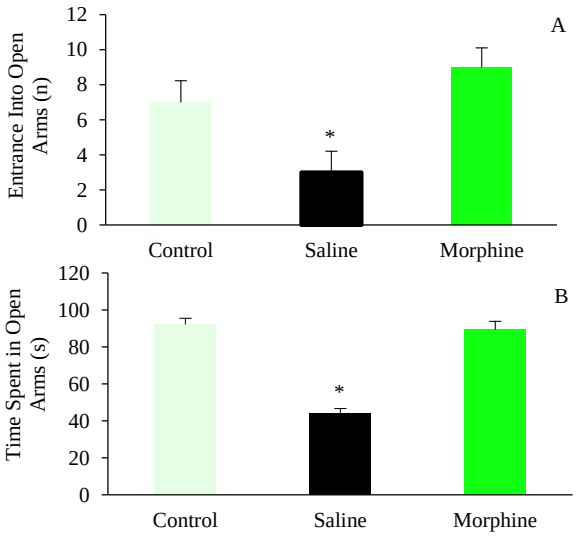

Figure 2. A) Time spent in open arm was significantly reduced in the saline group, while morphine-treated rats had no significant difference from naive control animals; B) number of entrance into the open arm was reduced in the saline-treated group. Morphine reduced to a decreased anxiety-like behavior following empathy for pain.
*P < 0.05 in comparison to naive animals

Hot plate: Threshold to thermal noxious stimulus was reduced in the saline-treated and morphine-treated groups in comparison to naive animals (ANOVA, $P < 0.05$). Furthermore, there was a significant difference between morphine and saline groups so that chronic morphine rats had a significantly lower nociceptive threshold in comparison to saline-treated animals as well (ANOVA, followed by Tukey's post-hoc, $P < 0.05$) (Figure 3).

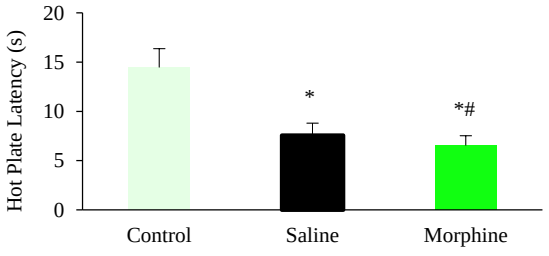

Figure 3. A significant reduction in thermal nociception was observed in saline-treated rats observing their cagemate in pain. Chronic morphine exposure led to even more reduced threshold.
*P < 0.05 in comparison to naive rats; #P < 0.05 in comparison to saline-treated animals

Tail flick: No significant difference was observed among study groups in this assay ($P > 0.05$, ANOVA) (Figure 4).

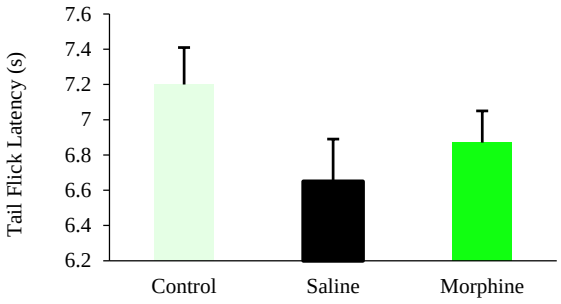

Figure 4. Empathy for pain did not alter the thermal nociception threshold at the spinal level in tail flick assay.

CPA score: Saline-treated pain observers had a significantly different CPA score in the CPA paradigm. Chronic morphine treatment reversed empathic effects on affective component of pain and there was not a significant difference between morphine and naive animals (Figure 5).

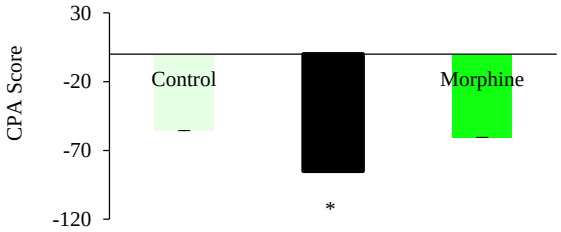

Figure 5. Conditioned place aversion (CPA) score was significantly different in saline-treated animals, so that they had a higher level of aversion for painful stimulus. Chronic exposure to morphine reversed this effect of empathy for pain on affective pain component.
*P < 0.05 in comparison to naive rats

Discussion

Empathy is the capability to mentally represent the feelings and mental states of other subjects. Due to the significant role of opioidergic processes in the empathy and the burden of addiction to morphine in society, the present study was performed to assay the effect of chronic administration of morphine on empathy-induced alterations in anxiety-like behaviors, nociception, and affective pain component. Findings of the study demonstrated that observing pain in a conspecies led to an increased anxiety-like

behavior and chronic exposure to morphine dampened this empathy-induced anxiety. Furthermore, empathy for pain leads to an increased pain aversion, which was reversed by chronic administration of morphine. Results of the current study demonstrate that chronic morphine dampens empathy-like responses through affective and not sensory pain component.

Nazeri et al. have demonstrated that acute opioid agonist therapy prior to the pain observation leads to a dampened empathy in the animals.[8] Rutgen et al. recruited placebo analgesia to evaluate the role of opioidergic pathway in humans. Their study demonstrated that opioids played a pivotal role in empathy for pain and pain pathways were activated in the same manner as the first-hand experience of pain.[9] Singer et al. have demonstrated that empathy for pain recruits affective and not sensory pain pathways.[20] Furthermore, van der Kam et al. have shown that morphine impacts the affective pain component in carrageenan-induced nociception. Chronic exposure to morphine reverses the anxiety-like behaviors following observation of pain in a conspecies and affective component of pain which was increased following observation of cagemate in pain had no significant difference in morphine-treated rats, thus demonstrating that chronic morphine plausibly alters affective pain component.[16] Furthermore, Nazeri et al. have previously demonstrated that empathy alters affective pain and this was verified in the current study. Interestingly, despite a reduced response to noxious stimuli observed following chronic morphine administration, affective pain component did not significantly change; thus, it might be implied that chronic morphine exposure alters empathy for pain through affective and not sensory pain pathways.[15]

Martinotti et al. evaluated empathy in alcohol-dependent subjects and demonstrated that both cognitive and emotional empathy were altered in these subjects. Since there are many similarities between alcohol and morphine addiction, especially the activation of limbic reward system, it seems plausible to extend the findings of that study to opium addicts as well and the current study revealed that exposure to morphine for a prolonged period altered empathic pain affection.[21]

Watanabe studied the effects of empathy on morphine conditioned place preference (CPP) and demonstrated that empathy for pain increased preference for morphine; thus, empathy for pain makes the animals more sensitive to rewarding effects of morphine.[22] Opioid receptors play an important role in mood regulation and affect within different brain regions. Nandigama and Borszcz have demonstrated that morphine injected directly into the amygdala of the rats led to affective analgesia, consistent with the findings of the present study, demonstrating that morphine administration might alter affective pain component in the empathy.[23] More studies are needed to elucidate the exact mechanisms involved and blockage of opioid receptors prior to empathy for pain in morphine-addicted animals might elucidate the exact mechanisms involved.

Vassileva et al. demonstrated that heroin abusers had a lack of empathy and presented with different psychopathic traits that are not commonly seen in normal population. This lack of empathic response due to abuse of heroin or vice versa is something that must be evaluated in future studies[14] and the findings of the current study might provide a basis to study the affective component of pain in empathy and also the plausible impact of different drugs of abuse on affective pain processing and empathy.

Regarding the neurobiology of morphine addiction, chronic abuse of morphine leads to a reduced oxytocin secretion in the brain. On the other hand, oxytocin is the major neurotransmitter involved in empathy; thus, it seems plausible that chronic administration of morphine dampens empathy-like behaviors through reduction in oxytocin secretion. Though this hypothesis was not tested in the current study, future studies might address the plausible role of oxytocin in empathy for pain and affective pain processing in opioid-dependent animals.[24]

One of the limitations in the current study is the use of male animals. Both pain and opioid addiction are sex hormone-dependent phenomena; thus, future studies might address the role of sex hormones in morphine-induced changes in affective pain in animal model of empathy.

Conclusion

Morphine dependence leads to a reduced empathy in rats and chronic morphine exposure reverses affective pain component changes following empathy for pain. Future studies

evaluating the role of different opioid receptor subtypes and also the possible involvement of oxytocin system and sex hormones in the animals are highly suggested.

Conflict of Interests

The authors have no conflict of interest.

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Authors' Contribution

First and corresponding author contributed to all the procedures. Other authors contributed to the collection of data, data analysis and manuscript preparation.

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کاهش جنبه عاطفی درد با وجود افزایش حساسیت به محرک‌های دردزا در مدل حیوانی هم‌دردی با تجویز مزمن مورفین

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مقاله پژوهشی

چکیده

مقدمه: هم‌دردی به عنوان قابلیت ادراک و بازسازی حالات ذهنی انسان‌های دیگر شناخته می‌شود. مطالعات پیشین نشانگر رابطه احتمالی بین اعتیاد به مورفین و مشتقات آن با اختلال در هم‌دردی در انسان‌ها می‌باشد. پژوهش حاضر به منظور ارزیابی تأثیر تجویز مزمن مورفین بر تغییرات حسی و عاطفی درد در مدل حیوانی هم‌دردی انجام شد.

روش‌ها: رت‌های نر نژاد ویستار سه ماهه در این مطالعه مورد استفاده قرار گرفت. حیوانات در گروه‌های دوتایی درون قفس (هرگروه هشت حیوان) نگهداری شدند. یکی از حیوانات به عنوان حیوان رنج کشنده و دیگری به عنوان مشاهده‌گر انتخاب گردید. حیوانات مشاهده‌گر به مدت ۸ روز، هر روز دو بار مورفین به صورت زیرپوستی با دز ۱۰ میلی‌گرم بر کیلوگرم دریافت کردند. در روز نهم، ۵۰ میکرولیتر فرمالین ۵ درصد به صورت زیرپوستی به کف پای حیوان رنج کشنده تزریق شد و داخل قفس کنار حیوان مشاهده‌گر قرار گرفت. رفتارهای شبه اضطرابی با استفاده از آزمون‌های Plus maze و Open field ارزیابی شد. حس درد به وسیله پلیت داغ و آزمون Tail flick مورد بررسی قرار گرفت. همچنین، از آزمون اجتناب مکانی شرطی جهت ارزیابی جنبه عاطفی درد استفاده شد.

یافته‌ها: حیوانات مشاهده‌گر که مورفین دریافت کرده بودند، سطح اضطراب کمتری را در مقایسه با گروه دریافت‌کننده سالین نشان دادند. با وجود کاهش آستانه تحمل درد حرارتی در تست‌های رفتاری درد، جنبه عاطفی درد متعاقب مشاهده درد در یک هم‌گونه سرکوب شده بود.

نتیجه‌گیری: تجویز مزمن مورفین و اعتیاد به مشتقات آن، منجر به تغییر هم‌دردی از طریق بخش‌های عاطفی و نه حسی درد می‌شود.

واژگان کلیدی: هم‌دردی؛ ادراک درد؛ اعتیاد به مورفین؛ رت‌ها

ارجاع: ناظری رضاآباد مسعود، جمال‌پور زهرا، عالم‌رجبی محمدصادق، نوذری معصومه، رضوی‌نسب معظمه‌السادات، نژادی اکرم. **کاهش جنبه عاطفی درد با وجود افزایش حساسیت به محرک‌های دردزا در مدل حیوانی هم‌دردی با تجویز مزمن مورفین.** مجله اعتیاد و سلامت ۱۳۹۹؛ ۱۲ (۴): ۲۵۱-۸.

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