



## Ginger Extract Reduces Chronic Morphine-Induced Neuroinflammation and Glial Activation in Nucleus Accumbens of Rats

Shima Torkzadeh-Mahani<sup>1</sup>, Saeed Esmaeili-Mahani<sup>2</sup>, Sima Nasri<sup>3</sup>,  
Fatemeh Darvishzadeh<sup>4</sup>, Reyhaneh Naderi<sup>1</sup>

### Original Article

#### Abstract

**Background:** Chronic usage of morphine elicits the production of inflammatory factors by glial cells and induces neuroinflammation. Ginger (*Zingiber Officinale* Roscoe) is a medicinal herb that has anti-inflammatory properties. It has been reported that ginger shows anti-addictive effects against chronic usage of morphine; however, its influence on morphine-induced neuroinflammation has not yet been clarified.

**Methods:** Morphine (12 mg/kg) was administrated intraperitoneally for 6 consecutive days. To evaluate the effect of ginger on morphine-induced neuroinflammation, ginger extract (100 mg/kg) was given orally 30 minutes before morphine. Glial fibrillary acidic protein (GFAP) and P38 mitogen-activated protein kinase (p38 MAPK) levels were assayed by immunoblotting in the rat nucleus accumbens (NAcc).

**Findings:** The injection of chronic morphine increased the levels of proteins involved in neuroinflammation (p38 MAPK and GFAP) in NAcc. Furthermore, the levels of p38 MAPK and GFAP significantly returned to the control levels by ginger extract.

**Conclusion:** The results suggest that the ginger extract can reduce morphine-induced neuroinflammation in NAcc.

**Keywords:** Morphine; Ginger; p38 Mitogen-activated protein kinases; Glial fibrillary acidic protein; Nucleus accumbens; Rats

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1- Department of Biology, School of Sciences, Shahid Bahonar University of Kerman, Kerman, Iran

2- Department of Biology, School of Sciences, Shahid Bahonar University of Kerman AND Laboratory of Molecular Neuroscience, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

3- Department of Biology, Payame Noor University, Tehran, Iran

4- Laboratory of Molecular Neuroscience, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

Correspondence to: Saeed Esmaeili-Mahani, Email: [semahani@uk.ac.ir](mailto:semahani@uk.ac.ir)

## Introduction

Opioids drugs, such as morphine, are used to manage pain over the past decades. However, long-term usage of these drugs induces side effects including addiction, tolerance, and physical dependence.<sup>1</sup> In addition, it has been documented that chronic usage of morphine leads to neuroinflammation in central nervous system (CNS), which is associated with the enhancement of morphine-induced antinociceptive tolerance, and physical and psychological dependence.<sup>2</sup> Morphine-induced neuroinflammation is commonly accompanied with the activation of glia, and production of inflammatory factors such as cytokines, chemokines, and surface antigens, which enhance immune response in the CNS.<sup>2,3</sup>

P38 mitogen-activated protein kinase (p38 MAPK) is one of the signal transduction pathways that regulate the production and release of inflammatory cytokines including interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). In addition, inflammatory cytokines induce further p38 MAPK activation in neuronal cells.<sup>4</sup> Previous studies have shown that chronic morphine induces glial activation through the p38 MAPK, which this signaling pathway leads to the release of several proinflammatory cytokines (such as TNF- $\alpha$  by astrocytes and microglia), and decreases subsequent morphine analgesia.<sup>5,6</sup>

It is clear that upregulation of glial fibrillary acidic protein (GFAP) is observed in the astrocytes after CNS injury, and it is known as biomarker of astrocytes activation.<sup>7-9</sup> It has been demonstrated that upregulation GFAP is significantly expressed in the CNS of morphine-treated animals, and such upregulation can be involved in the development of opioid side effects.<sup>3,10</sup>

Recently, herbal products have attracted the attention of scientists in herbal medicine.<sup>11</sup> Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been used in foods as a spice, and as a medicinal plant in traditional herbal medicine since ancient times. Ginger has been prescribed traditionally for the treatment of various diseases including fever, headache, diarrhea, nausea, infection diseases, arthritis, and rheumatic disorders.<sup>12,13</sup> Numerous studies have shown that ginger has various biological activities including anti-inflammatory, anti-oxidative, antimicrobial and anticancer activities.<sup>12,14,15</sup>

It is well demonstrated that ginger and its bioactive components have analgesic and anti-inflammatory properties. Ginger and its bioactive constituents directly suppress the proinflammatory cytokines and chemokines at the sites of inflammation. It has been reported that ginger anti-inflammatory activity can be performed through the modulation biochemical pathways in chronic inflammation.<sup>16,17</sup>

We have recently reported that ginger has an anti-addictive property in morphine-treated rats.<sup>18</sup> However, the effect of ginger on morphine-induced neuroinflammation has not been determined. The present study was performed to evaluate the effect of ginger on proteins involved in neuroinflammation (p38 MAPK and GFAP) in the nucleus accumbens (NAcc) of rats.

## Methods

**Animals:** Male Wistar rats (weight of 230-250 g) were housed in a photo period controlled room (12-hour light/dark cycle) with temperature of  $22 \pm 2$  °C. The animals had free access to food and water. The experimental protocol was firstly approved by the Animal Research Ethics Committee of the Kerman Neuroscience Research Center, Kerman, Iran (EC/KNRC/90).

**Drugs and injections:** Fresh ginger was prepared from the local market in Kerman City, Iran. The rhizome of herb was dried in air and ground into fine powder, and then extracted with 1 liter of ethyl alcohol 80%. A little of the plant extract were weighed and dissolved in physiological saline. The rats received 100 mg/kg of ginger extract intragastrically (i.g) 30 minutes before 12 mg/kg morphine which was injected intraperitoneally (once daily for 6 days). This dose was chosen according our previous study<sup>18</sup> as effective anti-addictive dose. Morphine hydrochloride was prepared by TEMAD CO. (Tehran, Iran) and dissolved in physiological saline.

**Western blot analysis:** Tissue samples from NAcc were homogenized in radioimmunoprecipitation assay (RIPA) buffer, and centrifuged at 14,000 rpm for 20 minutes at 4 °C. Equal amounts (40  $\mu$ g) of protein were electrophoresed using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), and then gently transferred to polyvinylidene difluoride (PVDF) membrane (Roche, Germany). After blocking (for 2 hours) with 5% non-fat dried milk in

Tris-buffered saline (TBS) with Tween 20 (blocking buffer, TBS-T, 150 mM NaCl, 20 mM Tris-HCl, pH 7.5, 0.1% Tween 20), the membranes were incubated with primary p38 and GFAP antibodies (1:1000) overnight at 4 °C. After washing in TBS-T (three times for 5 min), the membranes were incubated for 1 hour with matched horseradish peroxidase-conjugated secondary antibody (1:10000, Santa Cruz Biotechnology, CA, USA). The antibody-antigen reactions were luminated using the enhanced chemiluminescence (ECL) system, and detected on Lumi-Film chemiluminescent film (Roche, Germany). Lab Works software (UVP, UK) was used to assess the blotting bands density.  $\beta$ -actin (1:10000) was also blotted as loading control. The values were reported as tested proteins/ $\beta$ -actin ratio for each rat. Immunoblotting was performed on the days 9 and 13 after injections.

Data were analyzed using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). One-way analysis of variance followed by post-hoc Tukey's test were recruited. The  $P$ -value  $< 0.05$  was considered statistically significant. The results were shown as mean  $\pm$  standard error of mean (SEM).

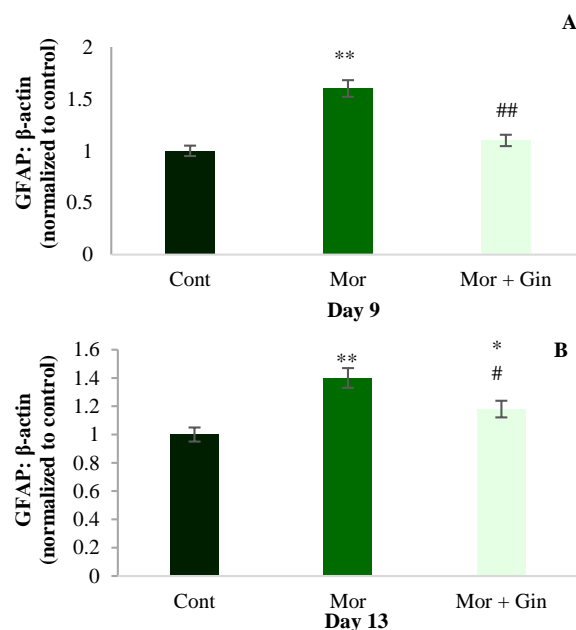
## Results

As shown in figure 1, following chronic administration of morphine, GFAP level significantly increased in NAcc ( $P < 0.01$ ) on the days 9 and 13 after injections (Figure 1-A and B, respectively). Increase in GFAP level induced by morphine was significantly reversed by ginger extract on day 9 ( $P < 0.01$ ) (Figure 1-A). In addition, ginger extract could significantly ( $P < 0.05$ ) suppressed GFAP protein upregulation on 13<sup>th</sup> day (Figure 1-B).

Immunoblot analysis showed that chronic morphine resulted in an elevation of p38 on 9<sup>th</sup> and 13<sup>th</sup> days after injections in rats' NAcc ( $P < 0.05$ ). The administration of an effective anti-tolerance and anti-addictive dose of ginger extract (100 mg/kg, i.g.) inhibited chronic morphine-induced p38 activation on day 13 ( $P < 0.01$ ) (Figure 2).

## Discussion

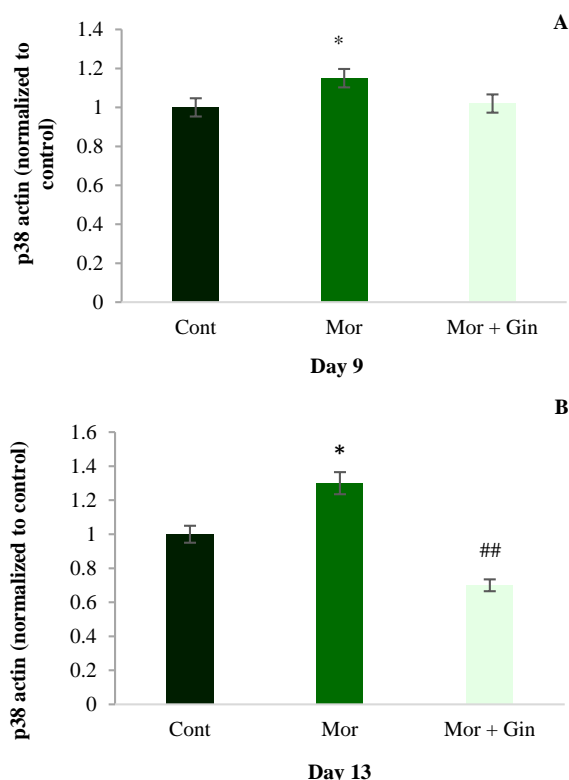
We have previously reported that ginger produces anti-addictive and anti-tolerance effects in morphine-injected rats.<sup>18</sup>



**Figure 1.** The levels of glial fibrillary acidic protein (GFAP) on 9<sup>th</sup> and 13<sup>th</sup> days following morphine injection in nucleus accumbens (NAcc) of control, chronic morphine-treated (12 mg/kg, intraperitoneally for 6 day) and morphine + ginger (12 mg/kg, intraperitoneally + 100 mg/kg, intragastrically) treated rats; beta-actin was used as an internal control. Values represent mean  $\pm$  standard error of mean (SEM). Cont: Control; Mor: Morphine; Gin: Ginger \* $P < 0.05$  and \*\* $P < 0.01$  versus control group; # $P < 0.05$ , ## $P < 0.01$  versus morphine-treated group

The present study examined the effect of ginger extract on neuroinflammation by assessing p38 and GFAP proteins expression in NAcc of rats. The data showed that ginger could decrease morphine-induced GFAP and p38 upregulation on 9<sup>th</sup> and 13<sup>th</sup> days after injections in the NAcc.

Morphine is a powerful opioid drug for treating pain but its long-term or chronic use activates astrocytes and microglia. Such activated glia can increase the release and promote gene expression of cytokines and chemokines, as well as elevate reactive oxygen species (ROS), which finally induce neuroinflammation in neural tissues. Neuroinflammation is involved in the intensification of antinociceptive tolerance and physical dependence induced by morphine.<sup>2,3,19</sup> Although it has been demonstrated that neuroinflammation leads to the release of neuroexcitatory and inflammatory cytokines; the underlying mechanisms involved in the induction of morphine-induced neuroinflammation have not yet been fully clarified.



**Figure 2.** Immunoblot analysis of p38 on days 9 and 13 in nucleus accumbens (NAcc) of rats that received morphine (12 mg/kg, intraperitoneally) alone and 100 mg/kg ginger intragastrically plus morphine; beta-actin was used as an internal control.

Values represent mean  $\pm$  standard error of mean (SEM).

Cont: Control; Mor: Morphine; Gin: Ginger

\* $P < 0.05$  versus control group; ## $P < 0.01$  versus morphine-treated group

It has been demonstrated that morphine administration induces astrocytes activation in some areas of the brain such as NAcc, lateral septal, locus coeruleus, caudate nucleus, and prefrontal cortex.<sup>20</sup> In addition, it has been reported that morphine leads to the activation of glia within the NAcc and subsequent upregulation of the expression of cytokines and chemokines, which oppose morphine-induced analgesia, and increase tolerance, respiratory depression, withdrawal, and reward to morphine.<sup>21</sup> Cooper et al. have reported that drugs such as opioids activate glial cells and the modulators of glial cells reduce opioid-induced tolerance and dependence, and conditioned place preference.<sup>22</sup>

In recent years, numerous documents have focused on the property of medicinal plants and their active components in treating illnesses. Ginger is a safe herbal medicine widely used in

around the world for the treatment of various disease such as arthritis, rheumatism, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, and infectious diseases. In addition, it has been reported that ginger shows beneficial effects as analgesic, neuroprotective, and anti-inflammatory agent.<sup>16</sup>

It is thought that ginger can modulate these activities through its main components (gingerols, shogaols, paradols, and zingerone). Previous studies have reported that ginger and its bioactive components play a fundamental role in the reduction of pain and inflammation. It has been documented that ginger inhibits proinflammatory cytokines, and decreases synthesis of proinflammatory prostaglandins and leukotrienes. It has been shown that ginger can suppress the phosphorylation of mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinase (JNK) pathways.<sup>16,17,23</sup>

It has been reported that ginger extract can inhibit morphine side effects such as addictive seeking behavior in rats.<sup>18</sup> Dedov et al. have been reported that ginger components function as agonists at vanilloid receptors, where present on pain afferents mediating joint pain.<sup>24</sup> It has been well reviewed that ginger shows analgesic and anti-inflammatory properties in clinical studies.<sup>17</sup> Therefore, it is possible that ginger exerts its biological effects through modulating the inflammation in the neural tissues.

It is well known that p38 MAPK pathway contributes to the overproduction, and release proinflammatory cytokines in CNS.<sup>4,25</sup> In addition, it has been reported that long-term usage of morphine activates p38 MAP cascade to promote morphine tolerance, which leads to opposing morphine analgesia.<sup>6,26</sup> We have previously reported that ginger extract has analgesic<sup>27</sup> and anti-tolerance<sup>28</sup> effects against morphine in rats. Jung et al. reported that ginger anti-neuroinflammatory effect is related to the suppression of p38 MAPK signaling pathway.<sup>27</sup> In addition, it has been shown that 6-gingerol suppresses the production of proinflammatory cytokines through the downregulating of p38 MAP kinase activity and nuclear factor kappa B (NF- $\kappa$ B) expression.<sup>28</sup>

It is well documented that opioids activate astrocytes and microglia in animal brain.<sup>29-31</sup> Chronic administration of morphine leads to astroglial hypertrophy and upregulation of GFAP levels in astrocyte cells.<sup>7</sup> GFAP is expressed in the CNS where known as a specific marker of astrocytes activity.

Morphine exposure enhances GFAP levels in different brain areas including ventral tegmental area, NAcc, and striatum as well as frontal cortex.<sup>22</sup> Studies have demonstrated that GFAP upregulation has a critical role in the induction of opioid tolerance and dependence.<sup>3,10</sup> In addition, it has been reported that a specific inhibitor of glial cells (fluorocitrate) reduces morphine-induced tolerance and analgesia, and also inhibits GFAP enhancement in spinal cord.<sup>7</sup>

## Conclusion

This study shows that ginger extract can attenuate NAcc protein levels involved in neuroinflammation induced by chronic usage of morphine. Therefore, it is possible that ginger anti-addictive effects is performed through the reducing glial activation and neuroinflammation.

## Conflict of Interests

The Authors have no conflict of interest.

## Acknowledgements

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## تأثیر کاهشی عصاره زنجبیل بر التهاب نورونی و فعال شدن گلیاهای ناشی از مصرف مزمن مورفین در هسته اکومبسن موش‌های صحرائی

شیما ترک‌زاده ماهانی<sup>۱</sup>، سعید اسماعیلی ماهانی<sup>۱</sup>، سیما نصری<sup>۲</sup>، فاطمه درویش‌زاده<sup>۲</sup>، ریحانه نادری<sup>۱</sup>

### مقاله پژوهشی

### چکیده

**مقدمه:** مصرف مزمن مورفین، موجب تولید شاخص‌های التهابی توسط سلول‌های گلیا و القای التهاب عصبی می‌شود. زنجبیل (*Zingiber officinale roscoe*) نوعی گیاه دارویی است که دارای ویژگی‌های ضد التهابی می‌باشد. اثرات ضد اعتیادی زنجبیل در برابر مصرف مزمن مورفین گزارش شده، اما هنوز تأثیر آن بر روی التهاب عصبی ناشی از مورفین مشخص نشده است.

**روش‌ها:** ۱۲ میلی‌گرم بر کیلوگرم مورفین ۶ روز متوالی به صورت داخل صفاقی تجویز گردید. جهت بررسی اثر زنجبیل بر التهاب عصبی ناشی از مورفین، ۱۰۰ میلی‌گرم بر کیلوگرم عصاره زنجبیل به صورت خوراکی (۳۰ دقیقه قبل از مورفین) مورد استفاده قرار گرفت. میزان پروتئین اسیدی فیبریلا گلیال (Glial fibrillary acidic protein یا GFAP) و پروتئین کیناز فعال شده میتوزن P۳۸ (P38 mitogen-activated protein kinases) یا p38 MAPK در هسته اکومبسن با کمک روش Western blot سنجیده شد.

**یافته‌ها:** تزریق مورفین مزمن، میزان پروتئین‌های درگیر در التهاب عصبی (GFAP و p38 MAPK) را در هسته اکومبسن افزایش می‌دهد. علاوه بر این، میزان GFAP و p38 MAPK توسط عصاره زنجبیل به طور معنی‌داری به سطح کنترل رسید.

**نتیجه‌گیری:** عصاره زنجبیل می‌تواند منجر به کاهش التهاب عصبی ناشی از مورفین در هسته اکومبسن شود.

**واژگان کلیدی:** مورفین، زنجبیل، پروتئین کیناز فعال شده میتوزن P۳۸، پروتئین اسیدی فیبریلا گلیال، هسته اکومبسن، موش‌های صحرائی

**ارجاع:** ترک‌زاده ماهانی شیما، اسماعیلی ماهانی سعید، نصری سیما، درویش‌زاده فاطمه، نادری ریحانه. تأثیر کاهشی عصاره زنجبیل بر التهاب نورونی و فعال شدن گلیاهای ناشی از مصرف مزمن مورفین در هسته اکومبسن موش‌های صحرائی. مجله اعتیاد و سلامت ۱۳۹۸؛ ۱۱ (۲): ۶۶-۷۲.

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۱- گروه زیست‌شناسی، دانشکده علوم، دانشگاه شهید باهنر کرمان، کرمان، ایران

۲- گروه زیست‌شناسی، دانشکده علوم، دانشگاه شهید باهنر کرمان و آزمایشگاه علوم اعصاب مولکولی، مرکز تحقیقات علوم اعصاب، پژوهشکده نوروفارماکولوژی، دانشگاه علوم پزشکی کرمان، کرمان، ایران

۳- گروه زیست‌شناسی، دانشگاه پیام نور، تهران، ایران

۴- آزمایشگاه علوم اعصاب مولکولی، مرکز تحقیقات علوم اعصاب، پژوهشکده نوروفارماکولوژی، دانشگاه علوم پزشکی کرمان، کرمان، ایران

Email: semahani@uk.ac.ir

نویسنده مسؤول: سعید اسماعیلی ماهانی