

*Original Article*

## The Effects of Angiotensin II and Captopril on Expression of Morphine Withdrawal Signs in Rat

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### Abstract

The mechanisms of drug dependence and rewarding properties of opiates are not exactly known and several neurotransmitters seem to be involved. It is possible that the rennin-angiotensin system could interact with the opioid system, since it has been shown that angiotensin II (Ang) and ACE inhibitors have analgesic, anticonvulsant and antidepressant effects and in some cases they could antagonize the effect of morphine. In the present study, the effect of Ang II and captopril on withdrawal signs was evaluated.

Male wistar rats were anesthetized and i.c.v cannula implanted and allowed to recover from surgery. Morphine was injected (i.p, 3 times a day) for 4 days to induce morphine dependence. The animals were divided into 3 groups and received saline, captopril, Ang II, and i.c.v, before naloxone injection. Naloxone precipitated morphine withdrawal signs, compared to the morphine dependent rats in saline, captopril and Ang II groups.

Results showed that in the captopril group, some of the withdrawal signs were significantly lower than the saline group ( $p < 0.05$  and  $p < 0.01$ ). In the Ang II group, some of the withdrawal signs were greater than the saline group ( $p < 0.01$  and  $p < 0.001$ ).

Considering the fact that captopril can reduce endogenous opioid degradation, it could probably reduce the morphine withdrawal signs in this way. On the other hand, captopril and Ang II can interact with dopamine, serotonin, substance p, acetylcholine or nitric oxide in different brain regions and alter morphine withdrawal signs.

**Keywords:** Captopril; Angiotensin II; Morphine withdrawal; Rat.

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### Introduction

The dopaminergic mesolimbic system that consist of ventral tegmental area (VTA), nucleus accumbens and medial prefrontal cortex, is considered to be crucial in the rewarding actions of opiates and involved in drug dependence (1, 2). Previous studies have found that the

effect of angiotensin II (Ang II) on learning and memory was abolished by a dopaminergic antagonist (pimozid)(3). In addition, disruption of the dopaminergic endings in discrete structure of the dopaminergic mesolimbic system confirmed the involvement of dopaminergic system on angiotensin II facilitation of learning and memory (3, 4). These data indicate that most cognition-improving effects of Ang II could be through the activation of dopaminergic mesolimbic system (3).

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The renin-angiotensin system (RAS) was initially described as a circulating humoral system influencing blood pressure, as well as the fluid and electrolyte homeostasis (5). But now it is well known that an independent RAS exists in the brain (6). Brain has its own intrinsic RAS, with all its components, and is capable of synthesizing angiotensin peptides and components of this system (5, 6). It has also been proposed that Ang II plays a neurotransmitters role in the central nervous system (CNS) (7). Ang II is involved in the regulation of other neurotransmitters such as GABA (8), noradrenaline, and 5-hydroxytryptamine (5-HT), as well as the inhibition of acetylcholine release (6). The angiotensin AT1 antagonist, losartan, was found to abolish the Ang II induced improvement in object recognition, thus the cognition–improvement effects of Ang II may be transmitted by AT1 (9). However, subsequent contradictory findings showed that losartan was also able to facilitate spatial and short-term memory, and could also reverse the scopolamine–induced cognitive deficits (10).

Angiotensin converting enzyme (ACE) inhibitors, such as captopril, enhance learning in rats and support the hypothesis that Ang II suppression may have cognitive enhancing effects (11). Experiments showed that Ang II inhibits acetylcholine release (12). Therefore, administration of ACE inhibitors could enhance acetylcholine release, and this effect may be responsible for the cognitive improvement (12).

The research for endogenous substances with anti-opioid activity has provided several evidences for morphine tolerance and morphine addiction. Among several of anti-opioid substances, cholecystokinin octapeptide (CCK-8) and Ang II are probably most attractive in CNS. Both of the small peptides have an abundant and widespread distribution in CNS. Ang II showed an anti-opioid activity as well as reversed morphine-induced analgesia in rats (13).

For example Ang II, injected icv, exerted a dose-dependent anti-nociceptive effect in the acetic acid-induced abdominal constriction test in mice (14) or Ang II, administered intrathecally, induced short lasting antinociceptive

effect in the rat (15). It is assumed that these effects are realized through an opioid mechanism and activation of AT1 receptor (16). These data suggest the participation of Ang II in transmission of nociceptive information and its interaction with opioid receptors (16). I.c.v administration of Ang II produced anti-nociceptive effects that could be blocked by pretreatment with naloxone (16).

Several evidences have shown that ACE inhibitors reduce the degradation of opioids and increase their level in the brain (17). In addition, ACE inhibitors have been reported to increase general health, vitality and work performance. A possible mechanism could be the release of beta-endorphins (18). It has been suggested that ACE inhibitors can alter the dopamine level in the brain (19) and beneficial effects of these drugs on Parkinson disease has been shown (19). The effect of ACE inhibitors on learning and memory (20, 21) have been investigated and shown that these effects are blocked by naloxone (22, 23). ACE inhibitors, commonly used to treat hypertension, are also used in the treatment of cocaine-abusing populations, based on their potential to reduce cocaine use by modulating the levels of dopamine and corticotrophin releasing factor in the brain (24).

Due to this evidence, further studies are needed to be carried out to elucidate the role of RAS in opiate reward and dependence. Therefore, in the present study we evaluated the effect of Ang II (main product of RAS) and captopril (ACE inhibitor) on morphine withdrawal signs in rat.

## Experimental

### *Animals and drugs*

Male wistar rats weighing 200-250 g (Razi institute, Tehran, Iran) were used in the present study. Animals were housed four to five per cage, with free access to food and water ad libitum, and maintained at  $22.0 \pm 2.0$  °C on a 12-light/dark cycle (light period 07:00 and 19:00 h). All the animals were allowed with the adapt to laboratory conditions for at last 1 week. The Isfahan University committee on animal research approved the experiments.

The drugs used were morphine (TEMAD Ltd., Teheran, Iran), Ang II (Sigma Co., St

Louis, USA), and captopril and naloxone (Daroo-Pakhsh Pharma, Iran). All the drugs were dissolved in saline solution.

#### *Intra-cerebroventricular cannula implantation*

Animals were anaesthetized with ketamine (150 mg/kg, i.p) and rampon (0.1 mg/kg, i.p) (25), then placed in a stereotaxic instrument (Stolting Instruments, USA). Stainless steel, 23-gauge-guide, cannula was implanted 1 mm above the right lateral cerebral ventricle. Sterotaxic coordinates were according to rat brain atlas of Paxinos and Watson (26) (0.9 mm posterior to the bregma, lateral+1.6 mm lateral to the sagittal suture and 3 mm from the top of skull). Cannula was fixed with dental acrylic cement, anchored by two screws placed in the skull. A stylet (26-gauge stainless steel) was placed into the guide cannula to allow the guide cannula to maintain patency. After surgery, rats were given 300,000 units of procaine penicillin G (i.p) to prevent infection. Animals were allowed 7 days to recover from surgery (27).

#### *Intra-cerebroventricular injection procedure*

For drug injection, the rats were gently restrained by hand. The stylet was removed from the guide cannula and a 27-gauge injection needle (1 mm beyond the tip of the implanted guide cannula) was inserted. The injection needle was attached to a 10  $\mu$ l Hamilton syringe by a polyethylene tube. The injection solutions were administered as a total volume of 5  $\mu$ l. The injection needle was retained in the guide cannula for an additional 60 s after injection, to facilitate diffusion of the drugs (28).

#### *Procedures*

To induce morphine dependence, morphine was administered i.p. (3 injections each day at 150 min intervals) for 4 days, in doses of 9, 16 and 25 mg/kg (1st day); 25, 25 and 50 mg/kg (2nd day), 50, 50 and 50 mg/kg (3rd day) and 50, 50 and 100 mg/kg (4th day). 180 min after the last morphine injection, the animals received naloxone (3 mg/kg i.p) and the signs of morphine withdrawal were measured (29). Ang II (1 nmol per rat) and captopril (300  $\mu$ /rat) were administered (i.c.v) 5 and 30 min before

the naloxone injection to captopril and Ang II groups, respectively. Then the animals were placed in plastic cylinders (50 $\times$ 18 cm) and the following signs were observed and evaluated for 30 min: the number of jumping, wet dog shakes, writhing, teeth chattering, grooming, genital grooming, standing and the percentage of weight loss before and 30 min after naloxone injection.

#### *Experimental design*

To evaluate the effects of captopril and Ang II on morphine withdrawal signs, 27 male rats (250-300 g) were used. The animals were divided into 3 groups: 1-saline group, which received morphine during 4 days and then received saline (5  $\mu$ l i.c.v) at the end of experiment (4th day) 30 min before the naloxone injection to precipitate withdrawal symptoms. 2-Captopril group, which received morphine for 4 days, and then received captopril (300  $\mu$ g i.c.v 30 min before naloxone. 3- Ang II group, which received morphine for 4 days, and then received Ang II (1 nmol in 5  $\mu$ l of saline i.c.v) 5 min before naloxone. At the end of experiment, all animals (on the 4th day) received naloxone (3 mg/kg, i.p) and withdrawal signs were recorded for 30 min.

#### *Data analysis*

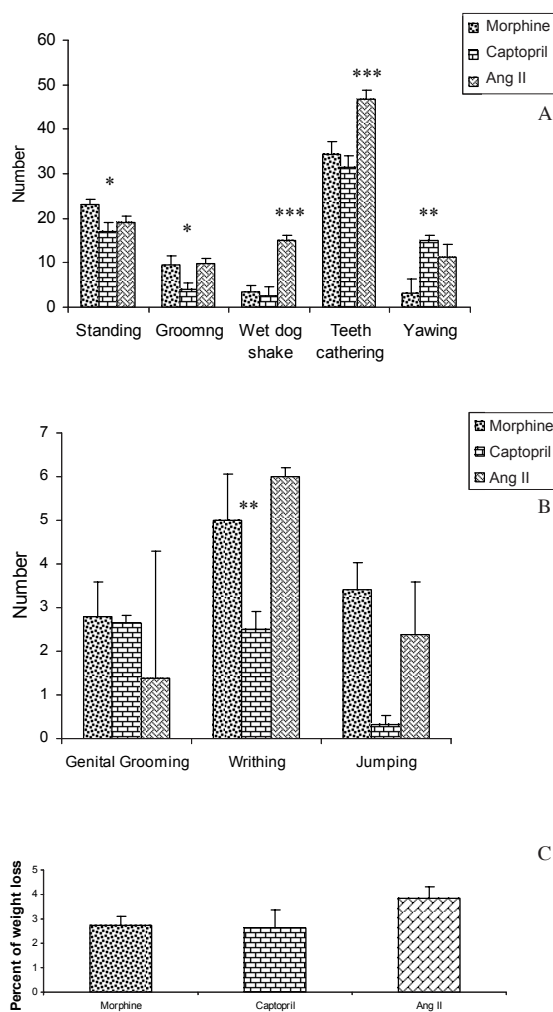
The overall treatment effects of the experiments were examined using a one-way analysis of variance (ANOVA) and post-hoc comparisons. The criterion for statistical significance was  $p < 0.05$ .

#### *Histology*

Immediately after the tests, all the rats were given 2  $\mu$ l of methylene blue in a lateral ventricle, anesthetized with a high dose of anesthetic and perfused with 100 ml of saline followed by 100 ml of formalin (10%) transcardially. The brains were removed and placed in formalin (10%). After 3 days, the brains were sliced into 60- $\mu$ m-thin slices. Data from rats with incorrect placement were excluded from the analysis (30).

## **Results and Discussion**

As shown in Figure 1, in the captopril group the number of standing, grooming (Figure 1A)



**Figure 1.** Comparison of morphine withdrawal signs among saline, Ang II and captoril groups. Data are presented as mean±SEM of the number of signs in 30 min . Only the weight loss data are presented as mean± SEM of percentage (n=8 in each group). \*P<0.05,\*\* P<0.01,\*\*\* P<0.001 compared to the saline group.

and writhing (Figure 1B), were significantly ( $p<0.05$  and  $p<0.01$ ) lower than that of the saline group ( $p<0.01$ ). Number of jumping was lower than that of the saline group, but the difference was not significant (Figure 1B). This shows that i.c.v injection of captoril could reduce morphine withdrawal signs in rats. The number of teeth chattering and wet dog shakes in the Ang II group was significantly greater than the morphine group (Figure 1A,  $p<0.01$  and  $p<0.001$ ). There was no significant difference in the percentage of weight loss in the 3 groups (Figure 1A).

In the present study, captoril injection

(i.c.v 300 µg) 30 min before the testing period, caused a decrease in morphine withdrawal signs (Figure 1). These findings are in agreement with the previous studies, which have shown that i.c.v injection of captoril in doses of 100, 300, 500 and 1000 µg could induce a dose dependent anti-nociceptive effect in rats, this effect was completely blocked by naloxone (10 mg/kg, i.p) (31). In the same study, it has been indicated that i.c.v administration of 300 µg of captoril also potentiated the anti-nociceptive effect of morphine in intact animals (31). Others have show that the anti-nociceptive effect of repeated doses of captoril and losartan were reversed by naloxone (32). It has been suggested that potentiation of morphine-induced anti-nociception by captoril is unlikely to be exerted through an effect on adrenal function and is most likely due to an increased brain endogenous opioid system (31). In our study, a decrease in withdrawal signs after injection of captoril may be due to the activation of endogenous opioid system in the brain. In several studies it has been shown that ACE inhibitors can activate this system (31). It is possible that this reduced withdrawal signs of morphine after captoril injection, could be influenced by the concentration of enkephalin in the brain. Other researchers have suggested that morphine could increase in a concentration dependent manner, the degradation of leu- enkephalin in bovine aortic endothelial cells. The enhanced leu-enkephalin degradation was due to an increase in the activity of ACE (33). On the other hand, it has been reported that endogenous opioid can reduce the withdrawal signs (34).

ACE can degrade substance P (17). We suggest that ACE inhibitors such as captoril may reduce degradation of substance P, thus increasing it in the brain. This could be another reason for a decrease in withdrawal signs. The others have confirmed the hypothesis that substance P could abolish morphine addiction in rats (35).

The effect of cholinergic system in morphine dependence has been investigated and proposed that an increase in cholinergic system activity in the brain can reduce morphine withdrawal signs (36). Decrease in morphine withdrawal by captoril may be related to an increase in acetylcholine in the brain.

Preliminary experiments with captopril, 0.3 mg/kg s.c, enhanced some of the naloxone-precipitated withdrawal signs such as rhinorrhea; lacrimation and salivation, but other withdrawal sign were not altered by either captopril treatment (37). But in our labratoy, captopril decreased some of the withdrawal signs such as standing, grooming, writhing and increased wet dog shake, which could be due to a difference in the method of administration.

The ACE activity in the rat brain was found to be decreased after implantation of morphine pellets, that was abolished by naloxone (38). This shows the existence of a permissive interaction between morphine and the renin-angiotensin system.

It has been reported that Ang II and its fragments have cognition-improving effects and facilitation of learning and memory process through an activation of the central dopaminergic and glutamergic systems in the mesolimbic and hippocampus (3). On the other hand it has been shown that the glutamergic and dopaminergic system in these regions have important roles in the opiate dependence (39, 40). Injection of Ang II (1 nmol) in morphine dependent rat could increase some withdrawal signs such as teeth chattering and yawing (Figure 1A).

Administration of Ang II [(i.c.v) (14) and intrathecally (16)] exerted anti-nociceptive effects that could be blocked by naloxone (16). It seems that these effects are realized through an endogenous opioid mechanism (16) and sometimes these effects were short lasting (16). Ang II also showed an anti-opioid activity, which is reversed by morphine-induced analgesia in rats (13).

Different mechanisms of the neuromodulatory action of Ang II on GABA release have been discussed (41). It is possible that in our investigation Ang II could interact with GABAergic system in the brain and increase some withdrawal signs in this way.

It has been shown that CRH can increase morphine withdrawal signs (42). on the other hand, it has been demonstrated that Ang II could increase CRH in the brain and captopril decreases it (10, 43). Increased morphine withdrawal signs by Ang II and it's decrease by captopril in the present study, may be due to an increase and

decrease in CRH release, respectively.

We suppose that an important site for the effect of Ang II in our study may be locus coeruleus (LC) nucleus, which contains considerable receptors for Ang II (44, 45) and has the most important role in opioid withdrawal (46).

Another mechanism could be the alteration in dopaminergic system activity. There are several evidences that RAS can alter dopaminergic activity in the brain (3, 7, 47, 48). The importance of this system in the rewarding property of morphine and drug dependence has been established (30, 49), but it is controversial and needed to be further investigated.

Finally, we propose that renin-angiotensin system could be involved in morphine dependence, but the mechanism need to be further investigated.

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