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Carbamazepine potentiates morphine analgesia on postoperative pain in morphine-dependent rats

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ABSTRACT

Postoperative pain and its control remain one of the most important issues in the field of surgery and health care systems. Morphine is a potent and effective analgesic, but substance abuse patients can manifest cross-tolerance to it, making it difficult to satisfy their analgesic/anesthetic requirements. As carbamazepine has shown antinociceptive properties in a variety of experimental and clinical settings, in the present study, we evaluated its potential antiallodynic effects on postoperative pain in naïve and morphine-dependent rats. Male rats were assigned to morphine-dependent and naïve groups and received intraperitoneally drug vehicles as control group, 3 mg/kg morphine, 5, 10 or 15 mg/kg carbamazepine or 5 mg/kg carbamazepine plus 3 mg/kg morphine as a combination therapy 2 and 24 h after surgery. Morphine-dependency was induced with multiple doses of morphine administered i.p. and plantar incision was made on the hind paw to simulate the postoperative pain. Paw withdrawal threshold (PWT) was obtained by von Frey filaments every 30 min after drug injection for up to 180 min. Morphine at 3 mg/kg exerted antiallodynic effects in naïve rats and a decreased antinociception was observed in morphine-dependent rats. In contrast, 5 mg/kg carbamazepine did not significantly alter PWT in naives but it was effective in dependent rats. 10 and 15 mg/kg carbamazepine attenuated allodynia following surgery in both groups. Co-administration of 5 mg/kg carbamazepine with 3 mg/kg morphine produced higher analgesia in morphine-dependent incised rats and prolonged antinociception as compared to morphine alone ($P<0.05$). Thus carbamazepine may potentiate the analgesic effect of chronically administered morphine on postoperative pain model in morphine-dependent rats.

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1. Introduction

Postoperative pain is a common type of pain (Sabetkasaei and Rezai Gharai, 2006) and one out of every two patients experiences intense or very intense pain during the first few days post-surgery (Whiteside et al., 2004). Postoperative care involves pain management, prevention and treatment of postoperative complications and recovery of function (Gilron, 2006). Injury and/or inflammation in peripheral tissues after surgery produces sensory changes resulting in prolonged pain, increased sensitivity to painful stimuli (hyperalgesia) and/or pain following innocuous stimulation (allodynia) (Girard et al., 2004). The standard treatment of severe postoperative pain is the use of opiates, which are also frequently abused. Morphine, a potent analgesic and mu receptor agonist, can cause physical dependence (Chisholm-Burns et al., 2007) and patients with morphine dependence can manifest cross-tolerance to other drugs, making it difficult to predict analgesic or anesthetic requirements (Katzung et al., 2007).

In the formalin induced model of pain, morphine-dependent rats experience significantly more severe pain behavior after incision compared to naïve rats (Rezai and Sabetkasaei, 2001) and that such pain can be poorly controlled with morphine administration. Thus, in order to boost the analgesia induced by morphine, co-administration of another agent able to produce analgesia by a different mechanism of action is often attempted (Girard et al., 2004).

Anticonvulsant agents, including carbamazepine, exert multiple pharmacological actions (Perucca, 2005). Carbamazepine has proved useful in managing trigeminal neuralgia and neuropathic pain (Gilron, 2006). Surgical nerve injury is indeed an important cause of neuropathic pain although mechanisms of postoperative and neuropathic pains are usually different. However, they share several similarities; the initiation and maintenance of both often involve sensitization of primary afferent and second-order dorsal horn neurons (Gilron, 2006; Woolf and Chong, 1993), both often manifest by hyperalgesia and allodyina at or near the affected sites (Coderre et al., 1993) and furthermore, excitatory amino acids such as glutamate

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play a major role in both of these conditions. Anticonvulsant mechanisms possibly involved in the modulation of postoperative pain by carbamazepine include Na^+ and Ca^{2+} channel blockade and suppression of glutamate release or an action on NMDA/AMPA receptors (Brennan et al., 2005; Gilron, 2006). One study suggested that carbamazepine suppresses either opioid tolerance or opioid withdrawal (Zullino et al., 2004).

Considering the high prevalence of morphine-dependency and the challenges in managing postoperative pain in such states, the present study aimed to evaluate the effect of carbamazepine on morphine induced analgesia on postoperative pain in naïve and morphine-dependent rats.

2. Materials and methods

2.1. Animals

Experiments on rats were approved by the ethical committee of Neuroscience Research Center of Shahid Beheshti University of Medical Sciences (Under the item: NRC-944). Male Wistar rats weighing 180–250 g were housed in groups of four under standard conditions with unrestricted access to food and water. Rats were housed in the room where the experimental procedure was to be performed in order to minimize the stress response to novel environmental cues. Animals were kept at a constant ambient temperature (24 ± 1 °C) under a 12-h light/dark cycle. All experiments were conducted according to the guidelines for investigation of experimental pain in conscious animals (Zimmermann, 1983).

2.2. Drugs

Morphine sulfate was obtained from Temad Iran Company (Iran) and dissolved in 0.9% physiological saline. Carbamazepine was supplied by Sobhan Darou Pharmaceutical (Iran) and suspended in 8 ml of propylene glycol and 2 ml of 3% Tween 80 solutions (Sakaue et al., 2005). Both drugs were administered intraperitoneally (i.p.) in a volume of 0.1 ml/100 gr.

2.3. Study design

2.3.1. Study groups

Experiments were conducted in 2 separate groups, including morphine-dependent and naïve rats which were further divided into 6 subgroups according to the drugs and the doses administered. All drugs were administered i.p. 2 and 24 h after intraplantar incision surgery.

Rats in both groups received either morphine 3 mg/kg, carbamazepine 5, 10 or 15 mg/kg, a combination of morphine3mg/kg with carbamazepine5mg/kg or drug vehicles (as control group). Vehicles included normal saline and propylene glycol–tween and were administered in control groups at the same volume as the treatment groups.

2.3.2. Study procedure

At the beginning, motor activity of all animals was assessed using rotarod test and the time duration they could keep coordination on rotating rod was recorded. Paw withdrawal threshold (PWT) was measured prior to the surgery as baseline and repeated 2 and 24 h following surgery (day 0 and 1). Immediately after the test procedure and 24 h after surgery drugs were administered, and then mechanical allodynia was assessed every 30 min up to 3 h at both days.

2.4. Induction of morphine-dependency

To induce morphine dependency, morphine solution was injected i.p. for 4 successive days. For the first two days, injections were made 3 times a day (8:30, 12:30, and 16:30 h), the first dose being 5 mg/kg, second dose 5 mg/kg and third dose 7.5 mg/kg at day 1; while these doses were respectively 7.5, 7.5 and 10 mg/kg on day 2. On day 3, morphine 10 mg/kg was injected twice at 8:30 and 16:30 h. Finally at day 4, morphine was injected 5 mg/kg as a single dose, and following a lapse of 120 min, the experiment was started. Naïve rats received saline for 4 days. On the fourth day, all animals could be operated as morphine-dependent rats and 120 min post-surgery, allodynia was evaluated. To verify the induction of morphine-dependency on the fourth day, naloxone 5 mg/kg (i.p.) was injected to a test batch and withdrawal symptoms including diarrhea, abdominal cramps, and occasionally jumping were assessed. This batch of animals was not further used in the study.

2.5. Postoperative pain model

The surgical method of Brennan et al. (1996) was used. Animals were anesthetized with diethyl ether. The left hind paw was cleaned with povidone iodine, and a 1-cm longitudinal incision (with a number 11 blade) was made through the skin and muscle of the plantar aspect of the hind paw. After homeostasis with gentle pressure, the skin was opposed with two mattress sutures of 5–0 nylon on HS-26 needle.

2.6. Rota-rod test

This test was used to rule out the possibility that the antinociceptive actions of carbamazepine and morphine due to non-specific alterations of the animals' locomotive activity. Prior to investigation of the antinociceptive effects of morphine and carbamazepine, the doses of the each drug alone and in combination that did not cause any signs of sedation or CNS depression were determined using the rotarod test (Cartmell et al., 1991; Goodchild et al., 2008). The rate of rotation was adjusted to allow the normal rats to stay on it for 180 s (7 rpm) for this apparatus (Ugo Basile, Model 7750, Italy). Each rat was given five trials before the actual reading was taken. The animals capable of staying on revolving rod for a period of 180 s before drug injection were selected and for evaluating the sedation/ataxia induced by drugs to be studied. The test was repeated 30 min after drug injection. The mean time durations when animals remained on the rotating bar for up to 180 s were compared among groups and impaired motor coordination was determined (Blackburn-Munro et al., 2002).

2.7. Evaluation of mechanical allodynia

Sensitivity to a mechanical stimulus was assessed with calibrated von Frey filaments (Stoelting, Wood Dale, IL) (Li et al., 2007). Animals were placed in individual plastic boxes on a wire floor and allowed to acclimatize for 15 min. Von Frey filaments were applied to the plantar surface of the hind foot and pressed to the point of bending over 6 s. The filaments were applied in increasing order of bending force until a brisk withdrawal or paw flinching occurred (cut off = 60 g). The lower paw withdrawal threshold (PWT) value obtained from 2 procedures, spaced at 2-min intervals was used for analysis. Graphs (PWTs vs times after injection) would be obtained in accordance to paw withdrawal threshold (PWT) data. Then overall effects of treatments were calculated by use of area under curve measurement (AUC) and bigger AUC meant more analgesia. Investigation of the effect of test compounds on mechanical allodynia was undertaken on surgery day and day one post-incision.

2.8. Statistical analysis

The effects of drugs on the nociceptive threshold were evaluated in a time course study as PWT, where each drug was administered at the time zero and then area under curve (AUC) obtained with

trapezoid method (on the basis of PWTs vs. time after drug injection curves). All data were expressed as mean ± S.E.M. (Standard Error of the Mean).

One way analysis of variance (ANOVA) followed by Tukey's test, was used for multiple comparison of vehicle-treated controls and drug-treated groups with SPSS software. Differences at $P<0.05$ were considered significant.

3. Results

3.1. Development of ataxia/sedation adverse effects of morphine and/or carbamazepine

The main limitation of morphine or carbamazepine for clinical uses is psychoactive side effects. Here, systemic daily treatment of animals with 3 mg/kg morphine or 5, 10 and 15 mg/kg carbamazepine was well tolerated by all rats as measured by endurance time on rotating rod (Table 1), however, higher doses of carbamazepine and co-administration of 3 mg/kg morphine with 10 or 15 mg/kg carbamazepine significantly attenuated time duration and ability to control motor coordination. Therefore, combination therapy was done only with 3 mg/kg morphine and 5 mg/kg carbamazepine.

3.2. Anti allodynic effect of morphine and/or carbamazepine on postoperative pain model

Intraplantar incision significantly reduced the nociceptive PWT of the incised hind paw, but there was no change in contralateral thresholds of the nonincised hind paw throughout the experiment period (data not shown). There was a significant difference between morphine-dependent and naïve controls in PWTs and AUC data during the period of observation. AUC in naïve control was 67 ± 4.62 and in morphine-dependent it changed to 29.92 ± 1.34.

As shown in Fig. 1 morphine was less effective in morphine-dependent rats than in naïve ones. Moreover, intraperitoneal administration of 5 mg/kg carbamazepine failed to ameliorate acute mechanical allodynia in naïve rats. In contrast, 10 and 15 mg/kg carbamazepine produced a marked attenuation of mechanical allodynia throughout the observation period in both groups in accordance to AUC data (Fig. 1). In fact, carbamazepine yielded a significant ameliorating effect on allodynia over the whole treatment period in both groups in a dose-dependent manner (Fig. 1). In addition, we assessed

Table 1
Effect of i.p. administration of morphine and/or carbamazepine on motor coordination by RotaRod test in naïve and morphine-dependent rats.

Group	Time(s)	S.E.M.
Naïve groups		
Control, naïve	164.8	5.9
Morphine 3 mg/kg	153.8	11.3
Cbz 5 mg/kg	148.8	11.2
Cbz 10 mg/kg	151.4	12.3
Cbz 15 mg/kg	135.4	13.2
Cbz 5 mg/kg + morphine 3 mg/kg	144.8	8
Morphine-dependent groups		
Control, morphine-dependent	159.4	6.5
Morphine 3 mg/kg	154.8	9.9
Cbz 5 mg/kg	153.8	9.1
Cbz 10 mg/kg	150.6	12.3
Cbz 15 mg/kg	148.8	10.1
Cbz 5 mg/kg + morphine3 mg/kg	139.2	11.5

Time(s) obtained from Rotarod test in naïve and morphine-dependent rats after i.p. injection of vehicles (Control), carbamazepine (5, 10 and 15 mg/kg), and morphine (3 mg/kg). The motor response or sedation was recorded 30 min after drug treatment up 180 s. Neither morphine 3 mg/kg nor carbamazepine (up to 15 mg/kg) significantly affected the motor response of animals as compared with control group ($P<0.05$). Statistical differences vs. control group were calculated using ANOVA, cbz: carbamazepine; S.E.M.: standard error of mean.

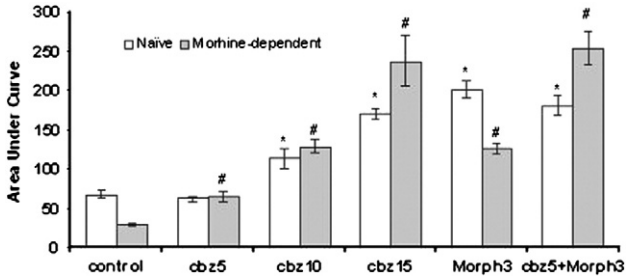

Fig. 1. The effects of intraperitoneal injection of 3 mg/kg morphine, 5, 10 and 15 mg/kg carbamazepine and co-administration on mechanical allodynia (n = 6 per group) using Area Under Curve data (obtained from PWT against time after drug administration curve) on a rat model of postoperative pain in morphine-dependent and naïve groups following drug injection on surgery day (day 0) and 24 h after surgery (day1). morph3: morphine 3 mg/kg; cbz5, 10 and 15: carbamazepine 5, 10 and 15 mg/kg. Values are expressed as mean ± S.E.M. *$P<0.05$ vs. naïve control; #$P<0.05$ vs. morphine-dependent control.

the antiallodynic effect of 3 mg/kg morphine co-administered with 5 mg/kg carbamazepine by AUC of PWT versus time after treatment and interestingly this combination therapy significantly increased total AUC (on both days) in naïve and morphine-dependent groups to 181 ± 12.65 and 254 ± 21.4 respectively.

3.3. Effect of morphine and/or carbamazepine on PWT after surgery in naïve rats

In a second set of analysis, we investigated time course of drug induced antinociception in a rat model of postoperative pain in naïve rats (Fig. 2A,B). As mentioned earlier, we applied daily injections of the drugs for 2 days starting at 2 h after surgery and monitored PWTs every 30 min up to 3 h after surgery.

Results of the analysis of postoperative pain using von Frey filament test showed a significant difference in PWT in naïve rats between day 0 and day 1 post surgery (Fig. 2A and B). In general, PWTs at day 1 were higher than day 0 in all groups.

Fig. 2A shows that in animals receiving 3 mg/kg morphine PWT significantly increased at 0.5, 1 and 1.5 h after injection on the surgery day and then returned to the control value. In contrast, 5 mg/kg carbamazepine failed to have significant antiallodynic effects at day 0 in naïve animals while combination therapy with 3 mg/kg morphine and 5 mg/kg carbamazepine was as effective as morphine alone.

Fig. 2B shows significant analgesic effects of 3 mg/kg morphine from 0.5 to 2.5 h after injection at day1 after surgery in naïve rats. 5 mg/kg carbamazepine did not exert antiallodynic effect on day 1 after surgery in naïve rats; however, co-administration with 3 mg/kg morphine was as effective as morphine alone in increasing the PWT.

3.4. Effect of morphine and/or carbamazepine on PWT after surgery in morphine-dependent rats

PWTs in morphine-dependent groups are illustrated in Fig. 3A and B at surgery day (day 0) and day after respectively. As shown in Fig. 3A, 3 mg/kg morphine or 5 mg/kg carbamazepine administration in morphine-dependent rats significantly increased PWTs until 1 h after drug injection at surgery day while this antiallodynic effect was present only 0.5 h following treatment at day 1 for both drugs alone (Fig. 3B). Surprisingly, co-administration of 3 mg/kg morphine with 5 mg/kg carbamazepine markedly attenuated the mechanical allodynia in morphine-dependent rats (Fig. 3A) in all time points at day 0. Similar effects were observed with the treatments at day 1 (Fig. 3B). Therefore, combination therapy caused effective long term reversal of allodynia in dependent rats.

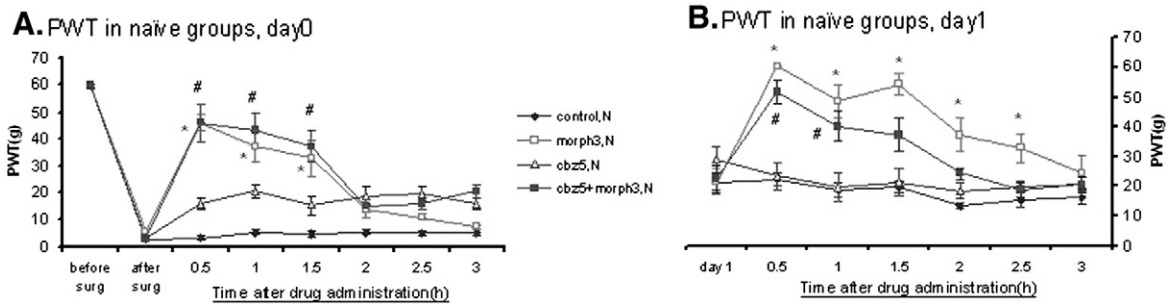

Fig. 2. Time course of the effect of intraperitoneal administration of 3 mg/kg morphine and/or 5 mg/kg carbamazepine on mechanical allodynia in a rat model of postoperative pain (n = 6 per group). Paw withdrawal thresholds (PWT) are plotted against the time after injection of the agents in naïve groups. (A) shows mechanical allodynia surgery day (day 0) and (B) illustrates mechanical allodynia 24 h after surgery (day 1). morph3: morphine 3 mg/kg; cbz5: carbamazepine 5 mg/kg, cbz5 + morph3: combination therapy; N: naïve rats. Results are expressed as mean ± S.E.M. *P<0.05 morphine group vs. control; #P<0.05 combination therapy vs. control.

4. Discussion

Postoperative pain management in patients with previous consumption or abuse of opioids, presents a complex problem regarding drug therapy (Rapp et al., 1995). There has been a growing interest in the potential utility of anticonvulsant drugs in the treatment of persistent pain. The present study therefore attempted to directly investigate the analgesic effect of carbamazepine or/and morphine in morphine-dependent and naïve rats on postoperative pain behaviors. Combination therapy was performed with 3 mg/kg morphine and 5 mg/kg carbamazepine, due to sedative/ataxic effect of higher doses of carbamazepine plus morphine.

No rat in this study responded to the highest force applied to the hind paw skin before incision but they all responded to the lower pressures after the incision, indicating that the incision produced mechanical allodynia, i.e., pain due to the stimuli that are not normally painful. Significant difference between morphine-dependent and naïve rats that received vehicle in PWTs and AUC data over the period of observation confirms higher pain sensitivity of dependent rats.

Morphine or carbamazepine significantly reduced mechanical allodynia, as compared to controls except for 5 mg/kg carbamazepine in naïve rats. This effect was dose-dependent with the greatest effect observed at the highest dose of carbamazepine. Numerous studies have verified the efficacy of morphine in the rat model of postoperative pain (Wang et al., 2000; Whiteside et al., 2004) because opioids modulate transmission of pain sensation in the spinal cord by decreasing the signal relayed from peripheral to central pain pathways and also alter the central perception of painful stimuli (Golan et al., 2007). Nevertheless, 3 mg/kg morphine was less effective in morphine-dependent rats on postoperative pain, suggesting that morphine alone could not produce an antiallodynic effect on the incisional pain in the rats rendered morphine-dependent with our protocol. Thus, it is conceivable that morphine tolerance occurs in morphine-dependent rats.

In case of carbamazepine, it has been associated with different mechanisms of action which, either individually or in combination, could be responsible for postoperative pain management. The antiallodynic action of carbamazepine could be explained by its proven block of voltage dependent sodium channels leading to stabilization of the presynaptic neuronal membrane and finally reduction in both neurotransmitter release (Zullino et al., 2004) and action potential conduction in nociceptive fibers (Catterall, 1987). Moreover, carbamazepine has been reported to interrupt glutamatergic function via N-methyl-D-aspartate (NMDA) receptor and, consequently, modulate central sensitization induced by the incision (Decosterd et al., 2004; Gilron, 2006). In addition, carbamazepine has been shown to be efficacious in acute and chronic pain management, treatment of trigeminal neuralgia and diabetic neuropathy (Campbell et al., 1966; Golan et al., 2007; Wiffen et al., 2011). Furthermore, carbamazepine had analgesic effects in the formalin test (Campbell et al., 1966) and demonstrated anti-inflammatory effect following postoperative pain (Bianchi et al., 1995).

Finally, co-administration of carbamazepine with morphine in morphine-dependent rats experiencing postoperative pain interestingly exerted effective and long term analgesia. Given the limited efficacy of any single drug administration and the multiple sites of action for analgesics, it is common in clinical practice to benefit from a drug combination approach in managing pain in order to obtain additive or supra-additive effects (Golan et al., 2007; Shannon et al., 2005). The observed effect of carbamazepine on postoperative pain in dependent animals suggests a direct action of this agent on morphine analgesia and confirms the ability of anticonvulsant administration in enhancing opioid analgesia or suppressing mechanisms of opioid tolerance as previously described (Gilron, 2006) and support opioid sparing effect of carbamazepine (Zullino et al., 2004).

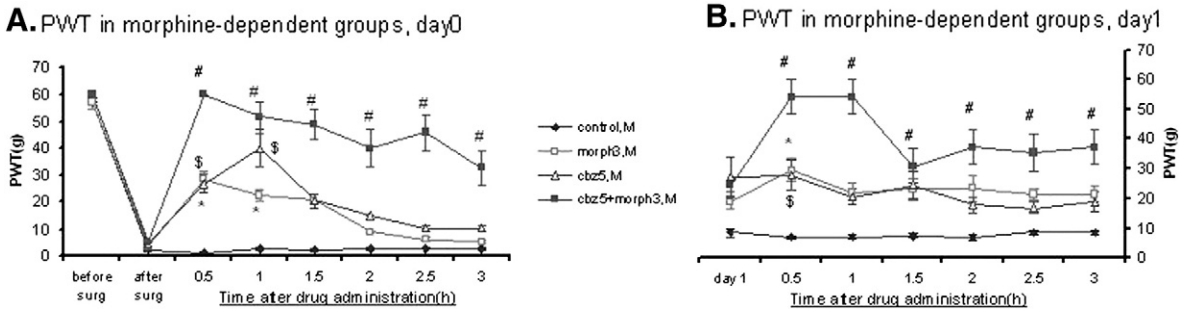

Fig. 3. Time course of the effect of intraperitoneal administration of 3 mg/kg morphine and/or 5 mg/kg carbamazepine on mechanical allodynia in a rat model of postoperative pain (n = 6 per group). Paw withdrawal thresholds (PWT) are plotted against the time after injection of the agents in morphine-dependent rats. (A) shows mechanical allodynia on surgery day (day 0) and (B) illustrates mechanical allodynia 24 h after surgery (day 1). Co-administration of 3 mg/kg morphine and 5 mg/kg carbamazepine significantly increased PWT throughout observation in morphine-dependent rats in postoperative pain model. morph3: morphine 3 mg/kg; cbz5: carbamazepine 5 mg/kg, cbz5 + morph3: combination therapy; M: morphine-dependent rats. Results are expressed as mean ± S.E.M. *P<0.05 morphine group vs. control; $P<0.05 carbamazepine group vs. control; #P<0.05 combination therapy vs. control.

Besides, according to the glutamatergic function of carbamazepine, these finding are consistent with studies which showed that NMDA receptor antagonists enhanced the antinociceptive effect of morphine (Sepúlveda et al., 2002; Wong et al., 1996). In addition, Pakulska reported that single administration of oxcarbamazepine enhanced the antinociceptive effect of morphine and led to a decrease in morphine tolerance in the hot plate test (Pakulska and Czarnecka, 2009) although Li et al. (2004) showed the inefficacy of carbamazepine on morphine tolerance in mice (Contreras et al., 1977). Such discrepancies can be due to the differences in protocols such as acute or chronic drug administration and test assessments (Chesler et al., 2002).

In morphine tolerance or dependence states, chronic administration of morphine up-regulates cyclic adenosine monophosphate (cAMP) which, in turn, stimulates protein kinase A (PKA), that phosphorylates and thereby activates both cAMP and voltage-gated sodium channels (Golan et al., 2007). Therefore, results of this study demonstrates that carbamazpine as a sodium channels blocker would block up-regulated sodium channels in morphine-dependency, and could decrease development of morphine tolerance or enhance and prolong morphine analgesia on incised rats. Further research is needed to identify the mechanism of action of carbamazepine in morphine dependency or tolerance.

5. Conclusion

Carbamazepine is an effective agent on postoperative pain management in naïve and morphine-dependent rats. In addition, result of combination therapy is potentially very useful clinically because many types of pain cannot be effectively treated with single agents such as morphine because of dose-related side effects and carbamazepine would potentiate and prolong the analgesic effect of chronically administered morphine on postoperative pain model in morphine-dependent rats.

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