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GAVIN PUBLISHERS

Archives of Palliative Care and Medicine

Research Article

Chou HH, et al. Arch Palliat Care Med: APCM-106.
DOI: 10.29011/APCM-106. 000006

Long Term Interactions between Tea Polyphenols, Memantine and Morphine on Orofacial Pain in Mice

His-Hsien Chou[1,2], Yu-Feng Huang[3,4], Hui-Wen Yang[3,4], Yu-Hsien Lee[3,4], Shoei-Yn Lin-Shiau[3*]

[1]School of Medicine, Chung Shan Medical University, Taiwan

[2]Department of Neurology, Chung Shan Medical University Hospital, Taiwan

[3]School of Dentistry, College of Oral Medicine, Chung Shan Medical University, Taiwan

[4]Department of Dentistry, Chung Shan Medical University Hospital, Taiwan

[*]**Corresponding author:** Shoei-Yn Lin-Shiau, School of Dentistry, College of Oral Medicine, Chung Shan Medical University, Taiwan. Tel: +866424718668 Ext: 55534; Fax: 866424759065; Email: syshiau@csmu.edu.tw

Citation: Chou HH, Huang Y, Yang H, Lee Y, Lin-Shiau S (2018) Long Term Interactions between Tea Polyphenols, Memantine and Morphine on Orofacial Pain in Mice. Arch Palliat Care Med: APCM-106. DOI: 10.29011/APCM-106. 000006

Received Date: 26 April, 2018; **Accepted Date:** 14 May, 2018; **Published Date:** 21 May, 2018

Abstract

Morphine is one of the analgesics used in dental clinics, but morphine tolerance is a severe side effect. We attempted to delay the development of morphine tolerance by a week off two days model and enhanced the analgesic effects of morphine by Green Tea Polyphenols (GTP), memantine (m) either alone or in combination (GTPm).

The results obtained showed that morphine was very effective in attenuating the orofacial pain induced by capsaicin in mice even after prolonged treatment in 92 days. GTP, memantine and GTPm all were effective in attenuating at the late stage of prolonged treatment in 92 days on the orofacial pain of mice. The behavioral changes in mice after chronic treatment of morphine included the increased locomotor activities and decreased the exploratory activities in the open field of elevated plus maze which could be apparently minimized by GTPm.

In conclusion, we have demonstrated that week off two days model and the combination use with GTPm could be successfully in enhancement of morphine analgesic effect on orofacial pain as long as for 3 months in the mice.

Keywords: Chronic Administration; GTP; GTPm; Memantine; Morphine; Orofacial Pain; Week off Two Days

Abbreviations

GTP : Green Tea Polyphenols

GTPm : Combination of Green Tea Polyphenol and Memantine

Introduction

The prevalence of orofacial pain in the dental clinic is estimated as high as about 25 % of the population in the world. Morphine is one of the most commonly used analgesics in dentistry [1]. However, the severe side effects of morphine analgesic tolerance limited of its use. It is urgent for us to investigate the better effective analgesic for treatment of orofacial pain.

Morphine is one of the opioid alkaloids from opium poppy [2]. It induced analgesic effects by acting on μ-receptors located at gabaergic nerve endings which subsequently activated the descending inhibitory serotonergic neurons at the brain stern and then produced analgesia. Moreover, morphine inhibited pain sensation by reducing the release of substance P, glutamate and nitric oxide from nociceptive afferent neurons at the spinal cord. Chronic morphine administrations may alter the μ-receptor-Gi protein-adenylate cyclase-cAMP signaling pathway which accounted for morphine analgesic tolerance.

Transient Receptor Potential Vanilloid 1 (TRPV1) is nonselective cation channels which could be activated by capsaicin isolated from hot chili peppers [3]. TRPV1 were highly expressed in trigeminal nerves, dorsal root ganglion cells and central nervous system (hippocampus, striatum, hypothalamus and cerebellum),

where it was involved in thermal nociception and burning sensation [4]. It has been demonstrated that TRPV1 colocalized with glutamatergic NMDA receptors and evoked pain sensation by facilitating activation of NMDA receptors. Memantine, an uncompetitive NMDA receptor antagonist, was thus able to attenuate pain sensation [5-7].

In this study, we attempted to delay the development of morphine tolerance by intermittent administration by week off two days model, which was based on our proposal that the processes of analgesic effects of morphine on μ-opioid receptors [8,9] may restore to the normal state during morphine holiday. The results obtained in this study were in accordance with our proposal that morphine analgesic effect on capsaicin-induced orofacial pain sustained as long as 92 days along with morphine administrations for 62 times.

According to the recent studies on the roles of neuroinflammation, oxidative stress and the activation of glutamate NMDA receptors in central nervous system involved in the development of morphine tolerance [10-14], we have tried in this study the effects of Green Tea Polyphenols (GTP) and memantine either alone or in combination (GTPm) on the analgesic effects of morphine and the morphine tolerance. This research approach was based on our previous findings that GTP possessed the pleiotropic effects including antioxidant, anti-inflammatory and neuroprotective effects [15-19], especially the potentiating effects of GTP on memantine (an uncompetitive antagonist of NMDA receptors) on neuroexcitability [20]. The results obtained in this study revealed that GTP and particularly GTPm alone exhibited not only analgesic effect but also enhanced that of morphine.

Materials and Methods

Animals

Adult male ICR (Institute for Cancer Research) mice 8-weeks old were used in this study. All mice were housed in groups of 5-7 in a cage with the same strain mates, in the animal faculty of the Chung Shan Medical University. Mice were allowed free access to food and water in a temperature controlled (22±1.5^{O}C) and relative humidity 50-70% environment maintained on a 12/12 hours light/dark cycle (light on 07:00 to 19:00). The experiment protocols were approved by the Animal Care Committee of Chung Shan Medical University (Approval No.1777).

Drugs

Memantine, capsaicin and morphine hydrochloride were purchased from Sigma-Aldrich Co. (St. Louis, Mo, USA).

Preparation of Green Tea Polyphenols (GTP)

One hundred grams of Chinese green tea, Longjing tea (produced by Wangs' Tea Enterprise Co., Ltd., Taipei, Taiwan), was suspended in 1 L of distilled water at 75°C for 30 min; then the supernatant was collected. This step was repeated three times. The supernatant was filtered to eliminate chlorophylls and undissolved particles. The total aqueous layers were concentrated to 0.5 L under reduced pressure using a rotary vacuum evaporator. The concentrated solution was extracted with an equal volume of chloroform three times to eliminate caffeine and pigments. The remaining aqueous phase was then extracted with an equal volume of ethyl acetate three times to extract tea polyphenols. The ethyl acetate was combined and evaporated in vacuum. The residue was dissolved in a small volume of distilled water and freeze-dried. This golden brown solid matter was called green tea polyphenols.

Drug Treatment of Mice

The following experimental design had 8 groups: (1) the control vehicle group; (2) the GTP group; (3) the memantine group; (4) the GTPm group; (5) the morphine group; (6) the morphine plus GTP group; (7) the morphine plus memantine group (8) the morphine plus GTPm group.

Green tea polyphenols (GTP 60 mg/Kg), memantine (Mem 10 mg/Kg), GTPm (GTP 30 mg/Kg plus Mem 3 mg/Kg) were dissolved in distilled water, which were orally administered to mice once per day and five times per week consecutively for 16 weeks. Morphine dissolved in saline was intraperitoneally injected (10 mg/kg/day) for consecutive five days and weekly off two days.

Nociceptive Assay

Orofacial pain was induced by injecting capsaicin (10 μg/5 μl) subcutaneously in vibrissa pad of mice and induced spontaneous orofacial pain response included 3 distinct patterns of acute grooming behaviors: fore-paw rubbing, lower lip skin/cheek rubbing against enclosure floor and hind paw scratching [21]. We record the total frequencies of orofacial pain response in 20 minutes after receiving capsaicin to quantify orofacial nociceptive level.

TruScan Photobeam Tracking

TruScan photobeam Tracking are used to record behavior (walking distance in margin and center area, number of times for jumping, rest time and total time of walking) of mice to compute emotional alteration. The tracking activity of depressed mice exhibits limited margin area walking distance; while normal mice distributes equally in margin and center area walking distance. Additionally, the tally of jumping and standing show the exploration and curious behavior of normal mice. One of the side effects of morphine is depressed mood, which causes reduction in locomotor activity and exploratory behavior. If memantine and GTPm can improve this side effect, locomotor activity and exploratory behavior will increase and the tracking in margin and center area will be equally distributed. TruScan photobeam Tracking will be measured 20 minutes after the injection of morphine.

Elevated Plus Maze Test

The elevated plus-maze test is one of the most widely used assessments to evaluate the anxiogenic-like behavior in rodents. The mouse was placed individually in the center of the maze (40 cm above the floor) facing an enclosed arm. The time spent in and number of entries into (with all 4 paws) both the open and enclosed arms (60 × 12 cm) were recorded for 5 min. The percentage of time spent in and the entries into the open arms was calculated by dividing the time spent in and the entries into the open arms by the total time spent in and the total arm entries into the both arms, respectively.

Statistics

Results for each experiment were represented as mean ± SEM. One-way ANOVA followed by a post-hoc t test was used to evaluate differences between the groups. The level of significance was defined as $p<0.05$.

Results

Effects of Drugs on Capsaicin-induced Orofacial Pain

As shown in Figure 1, the responses (frequencies of face rubbing or scratching) to orofacial pain could be reduced by GTP and memantine either alone or in combination. After the long term oral administration (92 days), GTPm exhibited not only a better analgesic by itself but also enhanced that of morphine. Memantine alone apparently exerted analgesic effects at earlier stage but gradually attenuated this effect.

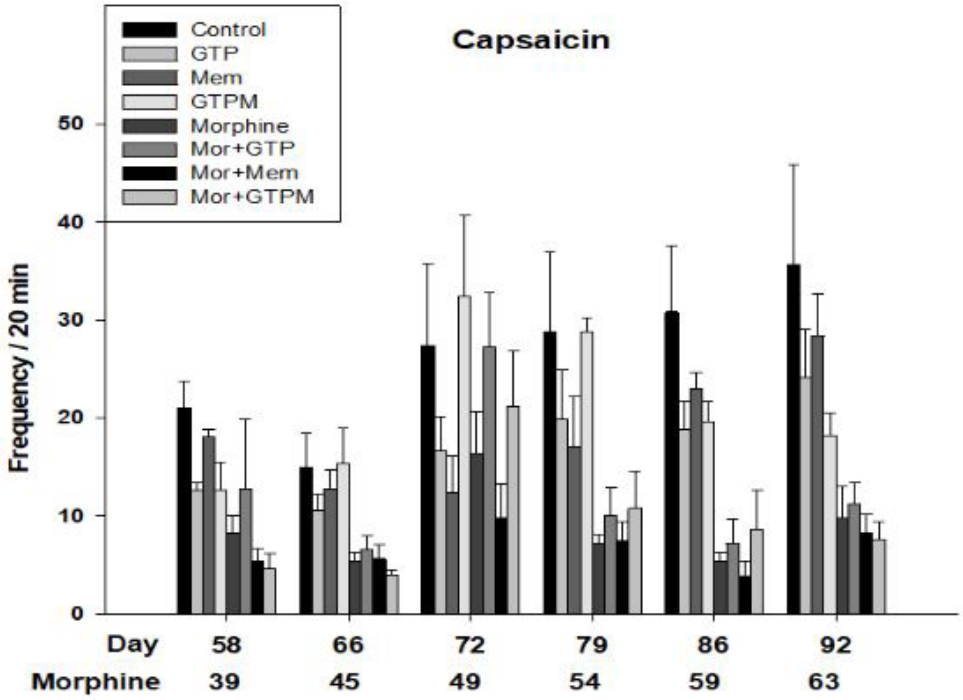

Figure 1: Effects of drugs on chronic administrations of morphine in mice.

GTP, memantine and GTPm alone were not only effective in attenuating orofacial pain induced by capsaicin but also enhanced analgesic effects of morphine.

Changes of Locomotor Activities of mice after Chronic Administrations of the drugs

As shown in Figure 2, GTP, memantine and GTPm had little effects on the locomotor activities (total distance) and the rest time (Figure 2A and Figure 2C). Memantine appeared to increase jump after 90 days administrations (Figure 2B). Morphine alone increased locomotor activities and decreased in jump activities and rest time after long term administrations. Memantine but not GTP nor GTPm enhanced morphine in increasing locomotor activities of the mice after 90 days (Figure 2A).

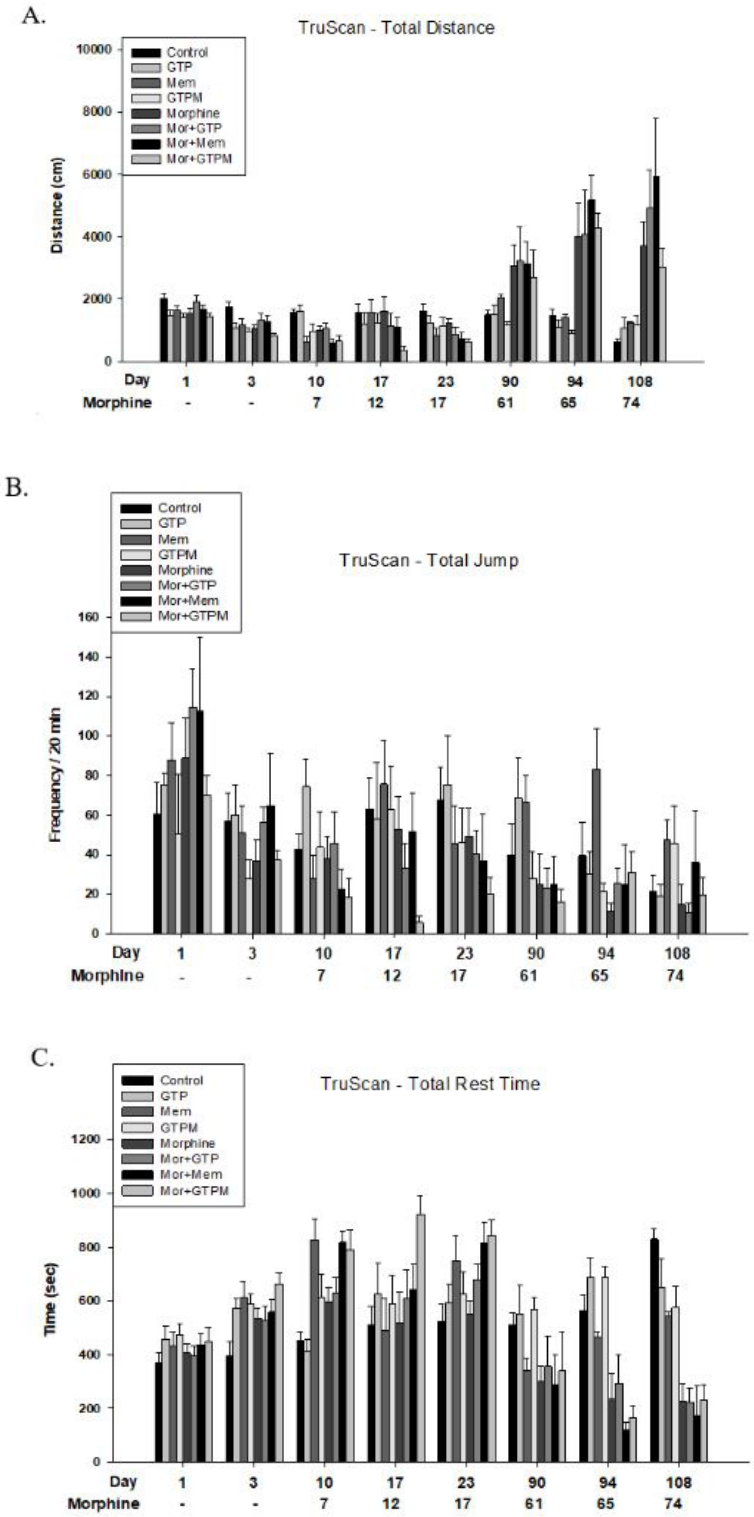

Figure 2: Behavioral changes of mice after chronic administration of drugs.

GTP, memantine and GTPm have little effect on locomotor activities but morphine markedly increased locomotor activities and decreased jump activities and rest time after 90 days. Memantine exacerbated but GTPm attenuated morphine in increasing locomotor activities.

Effects of Long Term Administrations of Drugs on the Exploratory Activities in the Elevated Plus Maze

The exploratory activities of the mice would increase its activities in the open field of the elevated plus maze apparatus, whereas the depressive mice would prefer to stay in the close field. As shown in Figure 3, GTP increased but morphine decreased the frequencies and time in the open field. Both of memantine and GTPm increased the frequencies in the open field and GTPm could counteract the decreased effects of morphine in the open field at later stage of 94 days.

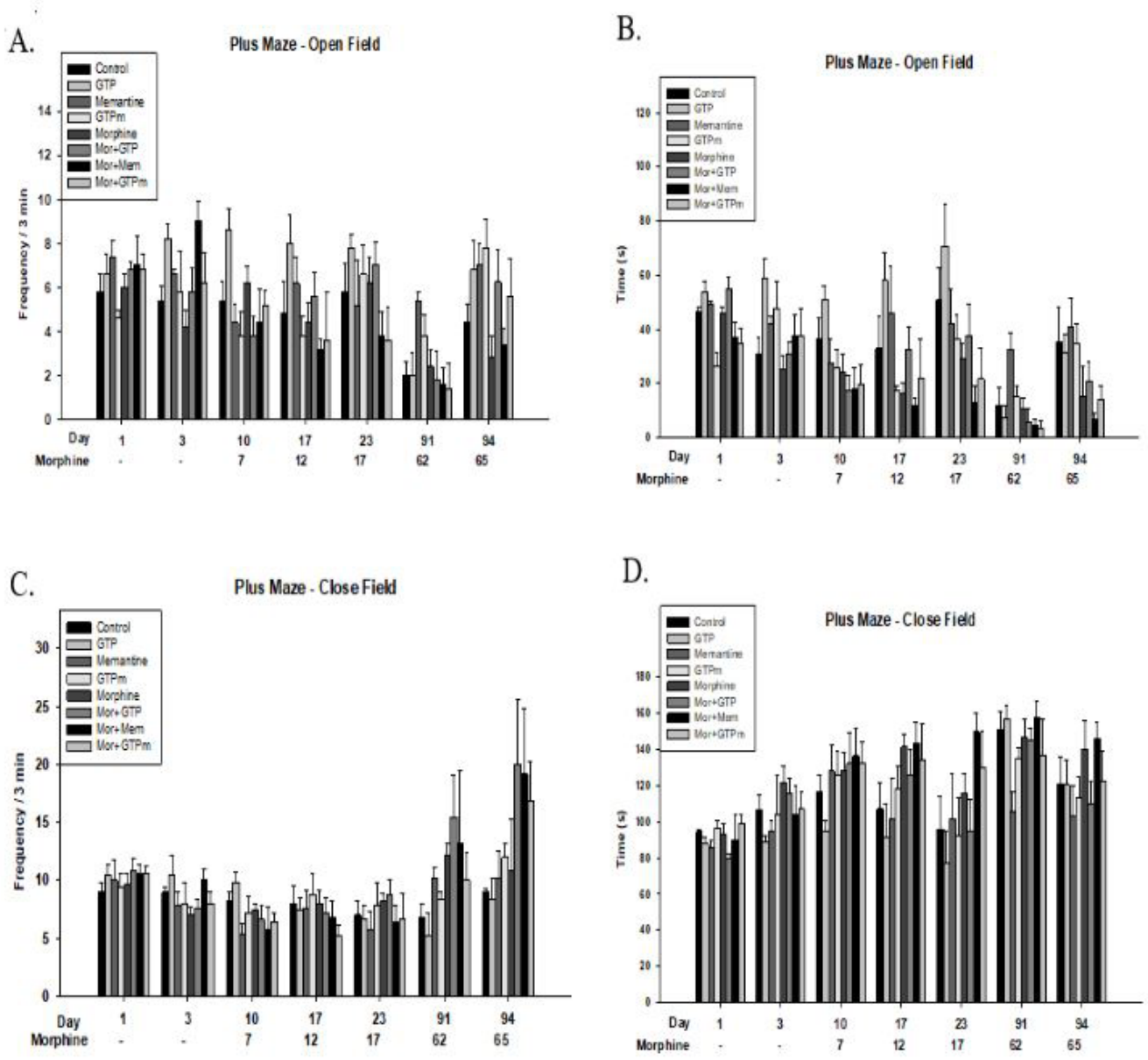

Figure 3: Effects of drugs on exploratory effects of mice in the elevated plus maze.

After prolonged treatment, morphine decreased the exploratory activities (both frequencies and time) in open field and increased time duration in close field, which could be attenuated by both GTP and GTPm.

Discussion

Morphine is an effective analgesic frequently used in dental orofacial pain therapy. The severe problem of morphine tolerance awaited to be solved. Based on the recent studies 4-8 of neuroinflammation, increased oxidative stress and the activation of NMDA receptors involved in the induction of morphine tolerance, we have designed a novel regimen of a composite (GTPm) containing GTP and memantine which was shown to be a promising enhancer of morphine analgesic effect on orofacial pain induced by capsaicin in mice.

The signaling pathways of μ-opioid receptors in central nervous system play important roles in morphine analgesic effects. It has been found that phosphorylation of μ-opioid receptors, coupling of G-protein with adenylate cyclase-cAMP system, receptor desensitization and receptor internalization, all were continuously increased which may account for the development of morphine tolerance. Based on these findings, we suggested that morphine holidays may be able to let the central nervous system to have repairing opportunities and restored to the normalized condition, so that morphine analgesic effect could be normalized. In this study, we have successfully demonstrated that the week off two days model effectively delayed morphine tolerance in mice, chronically treated with low dose (10mg/kg/day) of morphine for 3 months. Since GTPm by itself is not only effective analgesic but also enhanced morphine analgesic effects, it is suggested that GTPm may be a promising adjunctive to morphine (low dose) in management of orofacial pain. Moreover, alternative application of nonopioid analgesic agents during morphine holidays and the combination use of morphine with other antioxidants (phytopolyphenols) with another NMDA receptor antagonist could be an ideal strategy to combat clinical chronic pain. This proposal is hopefully validated in the near future.

Conclusion

We have demonstrated that week off two days model and the combination use with GTPm could be successfully in maintenance of morphine analgesic effect on orofacial pain as long as for 3 months. The implication of this finding is that low dose of morphine in combination of antioxidants (such as GTP or phytopolyphenols) with NMDA receptor antagonists (memantine or others) and week off two day model (alternative use of non-opioid analgesic during morphine holidays) could possibly delay the development of morphine analgesic tolerance in clinical patients

Acknowledgements

The authors greatly appreciate former dean professor Mingyung Chou for his continuous support of this research.

References

1. Docherty MJ, Jones III RCW, Wallace MS (2011) Managing pain in inflammatory bowel disease. Gastroenterol Hepatol 7: 592-601.
2. Ghelardini C, Mannelli LDC, Bianchi E (2015) The pharmacological basis of opioids. Clin Cases Miner Bone Metab 12: 219-221.
3. Xu W, Liu J, Ma D, Yuan G, Lu Y, et al. (2017) Capsaicin reduces Alzheimer-associated tau changes in the hippocampus of type 2 diabetes rats. PloS one 12: e0172477.
4. Zhang H, Jia D, Wang Y, Qu L, Wang X, et al. (2017) Enhanced ability of TRPV1 channels in regulating glutamatergic transmission after repeated morphine exposure in the nucleus accumbens of rat. Brain Res 1660: 47-57.
5. Aiyer R, Mehta N, Gungor S, Gulati A (2018) A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. Clin J Pain 34:450-467.
6. Morel V, Joly D, Villatte C, Dubray C, Durando X, et al. (2016) Memantine before mastectomy prevents post-surgery pain: a randomized, blinded clinical trial in surgical patients. PloS one 11: e0152741.
7. Wu BT, Chen KT, Liu KS, Chen YW, Hung CH, et al. (2015) Clonidine intensifies memantine cutaneous analgesia in response to local skin noxious pinprick in the rat. Pharmacol Rep 67: 485-489.
8. Corder G, Tawfik VL, Wang D, Sypek EI, Low SA, et al. (2017) Loss of μ opioid receptor signaling in nociceptors, but not microglia abrogates morphine tolerance without disrupting analgesia. Nat Med 23:164-173.
9. Grace PM, Maier SF, Watkins LR (2015) Opioid-induced central immune signaling: implications for opioid analgesia. Headache 55: 475-489.
10. Creeley CE, Wozniak DF, Nardi A, Farber NB, Olney JW (2008) Donepezil markedly potentiates memantine neurotoxicity in the adult rat brain. Neurobiol Aging 29: 153-167.
11. Hassanipour M, Amini-Khoei H, Shafaroodi H (2016) Atorvastatin attenuates the antinociceptive tolerance of morphine via nitric oxide dependent pathway in male mice. Brain Res Bull 125:173-180.
12. Ozdemir E, Bagcivan I, Durmus N, Altun A, Gursoy S (2011) The nitric oxide-cGMP signaling pathway plays a significant role in tolerance to the analgesic effect of morphine. Can J Physiol Pharmacol 89: 89-95.
13. Laursen JC, Cairns BE, Dong XD, Kumar U, Somvanshi RK, et al. (2014) Glutamate dysregulation in the trigeminal ganglion: a novel mechanism for peripheral sensitization of the craniofacial region. Neuroscience 256: 23-35.
14. Kayser V, Latre´molie`re A, Hamon M, Bourgoin S (2011) N-methyl-D-aspartate receptor-mediated modulations of the anti-allodynic effects of 5-HT1B/1D receptor stimulation in a rat model of trigeminal neuropathic pain. Eur J Pain 15: 451-458
15. Lin YL, Juan IM, Chen YL, Liang YC, Lin JK (1996) Composition of polyphenols in fresh tea leaves and associations of their oxygen-radical-absorbing capacity with antiproliferative actions in fibroblast cells. J Agric Food Chem 44: 1387-1394.

16. Lin JK (2002) Cancer chemoprevention by tea polyphenols through modulating signal transduction pathways. Arch Pharm Res 25: 561-571.

17. Lin JK, Lin-Shiau SY (2006) Mechanisms of hypolipidemic and antiobesity effects of tea and tea polyphenols. Mol Nutr Food Res 50: 211-217.

18. Deng YT, Lin JK (2011) EGCG inhibits the invasion of highly invasive CL1-5 lung cancer cells through suppressing MMP-2 expression via JNK signaling and induces G2/M arrest. J Agric Food Chem 59: 13318-13327.

19. Huang HC, Lin JK (2012) Pu-erh tea, green tea, and black tea suppresses hyperlipidemia, hyperleptinemia and fatty acid synthase through activating AMPK in rats fed a high-fructose diet. Food Funct 3: 170-177.

20. Chen CM, Lin JK, Liu SH, Lin-Shiau SY (2008) Novel regimen through combination of memantine and tea polyphenol for neuroprotection against brain excitotoxicity. J Neurosci Res 86: 2696-2704.

21. Madasu MK, Okine BN, Olango WM, Rea K, Lenihan R, et al. (2016) Genotype-dependent responsivity to inflammatory pain: a role for TRPV1 in the periaqueductal grey. Pharmacol Res 113: 44-54.