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Vigabatrin attenuates the development and expression of tolerance to morphine-induced antinociception in mice

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ABSTRACT

The efficacy of opioids is limited in chronic pain treatment, as a result of development of opioid tolerance. Based on previous demonstration of the effect of anticonvulsant drugs on morphine antinociception, the present study investigated the effects of vigabatrin (VGB) on the development and expression of morphine tolerance in mice. 101 male NMRI mice weighing 20–25 g were used in these experiments. To evaluate the VGB effects on the development or expression of morphine tolerance, animals received VGB (5, 10 or 20 mg/kg; i.p.), 30 min before morphine (50 mg/kg; s.c.) during induction period once daily for 3 days; or 30 min before challenge dose of morphine (5 mg/kg) before and after morphine-induced tolerance, respectively. The analgesic effect of VGB was evaluated at 30-time intervals (30, 60, 90 and 120 min) by tail-flick analgesiometer. The results showed that VGB at the dose of 20 mg/kg significantly attenuated the development and expression of morphine tolerance. Additionally, VGB alone did not affect the tail-flick latency times. Therefore, while VGB alone has no antinociceptive effect, it can prevent the development of morphine tolerance in mice.

1. Introduction

Opioid analgesics, such as morphine, are commonly used for the treatment of severe and chronic pain. However, long-term efficacy of morphine is often limited because of the opioids' side effects such as significant nausea, drowsiness, dizziness and development of abnormal sensitivity to pain or paradoxical hyperalgesia (Brodner and Taub, 1978; Eisenberg et al., 2005; Haghparast et al., 2008a,b). Opioid tolerance can significantly hamper the effective treatment of chronic pain with opioid analgesics (Bie and Pan, 2005; Nestler, 2004). Tolerance is defined as the phenomenon whereby exposure to opioids results in attenuation of the effect or requirement of a larger dose to produce the same effect (Gutstein and Akil, 2001). Whereas the conditions required for the development of human opioid tolerance are unclear (Gram et al., 1988), this phenomenon is particularly robust in experimental models of acute nociception (Jhamandas et al., 2000).

On the other hand, it is highly interesting that several anticonvulsant drugs which commonly used for treating 'fits' or epilepsy are also effective for treating pain (Orii et al., 2003). Most recognized anticonvulsant mechanisms which are involved in the central desensitization are also important in postoperative pain relief (Woolf and Chong, 1993). Recent evidence suggest that anticonvulsants might decrease opioid consumption either by enhancing opioid analgesia or by suppressing mechanisms of opioid tolerance (Gilron, 2006). For example, gabapentin has shown increased opioid antinociceptive effect in both animal (Powell et al., 1999; Shimoyama et al., 1997) and human models (Eckhardt et al., 2000) of brief thermal pain as well as in animal (Matthews and Dickenson, 2002) and human neuropathic pain (Gilron et al., 2005). Moreover, anticonvulsants are also useful in the treatment of acute pain conditions (Thienel et al., 2004) because they reduce cell membrane excitability in central and peripheral fibers.

Vigabatrin (VGB) is a GABA analogue, which binds covalently to active sites of GABA aminotransferase resulting in an increase in GABA levels in the brain (Abdulrazzaq et al., 2005). Although VGB usage has been restricted due to defects on the visual field (Eke et al., 1997) but an important consequence is that there is no evidence concerning the development of tolerance to VGB (Tamayo and Contreras, 1983). Additionally, the antinociceptive effect of VGB has been demonstrated in the animal model of chronic neuropathic pain (Alvez et al., 1999; Czuczwar et al., 2001). It seems that further investigations regarding VGB-induced antinociception are required to better understand its analgesic role in the acute pain model. Based on these findings, the

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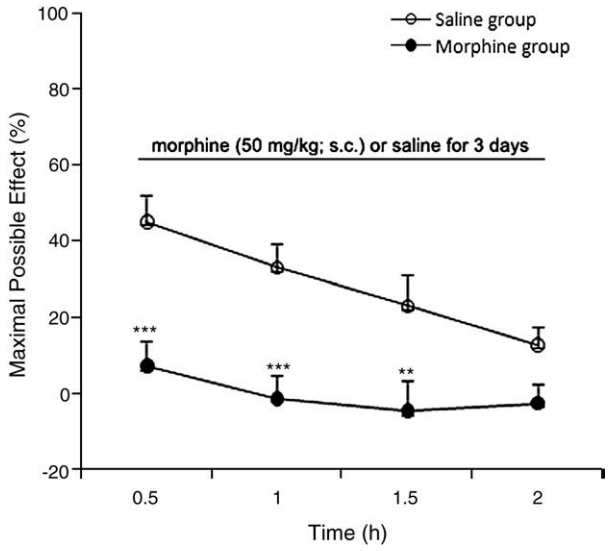

Fig. 1. The effect of challenge dose of morphine (5 mg/kg; s.c.) following 3 consecutive days administration of saline (○) or morphine (●) as an induction period. Each point is the mean ± SEM of percent of maximal possible effect (%MPE) for 7–8 mice. *$P<0.05$, ***$P<0.001$ compared to the saline-treated group.

objective of this study was to evaluate the antinociceptive response of VGB alone and its effect on the development and expression of tolerance to morphine-induced antinociception in the acute model of pain, using tail-flick test in mice.

2. Materials and methods

2.1. Animals

The experiments were performed on adult male NMRI mice (Pasteur Institute, Iran) weighing 20–25 g. They were housed seven per cage in a room adjacent to the testing room, and maintained on a 12/12-h light/dark cycle (lights on at 07:00 h) and kept at constant temperature (22 ± 2 °C). Following a 45-min acclimatization period, experiments were conducted between 14:00 and 17:00 h, during the light portion of the cycle. Animals were allowed free access to food and water except during the experiments. All experiments were executed with the Guide for the Care and Use of Laboratory Animals (National Institute of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University, M.C.

2.2. Drug administration

Morphine sulphate (Temad Co, Iran) and vigabatrin (Sigma-Aldrich, USA) were dissolved in saline. The VGB and morphine were prepared immediately just before use and injected intraperitoneally (i.p.) and subcutaneously (s.c.) in a volume of 10 ml/kg, respectively.

2.3. Assessment of morphine antinociception

Nociception was assessed with the tail-flick apparatus (D'amour and Smith, 1941). Tail-flick latency (TFL) is a spinal response and, therefore, TFL is a measurement of pain threshold at the spinal level. Mice were wrapped in a towel and placed on the apparatus. Small area of the tail was exposed to the lamp at 2 cm from the distal end. Lamp intensity was adjusted to produce a baseline latency of 2–4 s. The tail-flick latency represented the period of time (s) from the beginning of the trial to the tail deflection. A cut-off time of 8 s was used to prevent tissue damage. Baseline latency was assessed in duplicate with 30-min intervals and recorded as an average of TFL time. TFLs (s) are expressed as percentage of maximal possible effect (%MPE) which was calculated from the following formula:

$$\%\mathrm{MPE} = \frac{\text{Post-drug latency (s)} - \text{Baseline latency (s)}}{\text{Cut-off value (s)} - \text{Baseline latency (s)}} \times 100.$$

2.4. Induction of morphine tolerance

The animals were rendered tolerant to morphine using the method by a previous study on the induction of morphine tolerance in mice (Zarrindast et al., 2002). Tolerance was induced on day 1 (after challenge dose of morphine testing) through day 3 by administering morphine (50 mg/kg; s.c.) once daily. In the fourth day, two tail-flick tests, as described in Section 2.3, were done for each mouse to average them as a baseline latency; then challenge dose of morphine (5 mg/kg; s.c.) was injected; 30 min after morphine injection two other tail-flick tests were done to average them to find post-drug latency for each mouse for evaluating the development of tolerance to morphine.

2.5. Experimental protocols

To assess the degree of tolerance, antinociceptive response to morphine was measured before (day 1) and after (day 4) the induction of morphine tolerance. The analgesic response to a challenge dose of morphine (5 mg/kg; s.c.) was determined by tail-flick test as a model of acute pain in mice ($n = 7$–8 in each group). In the morphine-treated mice after induction of morphine tolerance, analgesic response to the challenge dose was determined again on day 4 at 30-min intervals (0.5, 1, 1.5 and 2 h) after the same morphine (5 mg/kg) injection on the first day. To evaluate the VGB effects on development or expression of morphine tolerance, animals received VGB (5, 10 or 20 mg/kg; i.p.), 30 min before morphine (50 mg/kg; s.c.) once daily for 3 days during the induction period or 30 min before challenge dose of morphine (5 mg/kg) before and after morphine-induced tolerance, respectively. In these groups, the antinociceptive responses of morphine in pre-induction (day 1) and post-induction (day 4) test days for each animal were also determined at the above time set interval by tail-flick test. In the saline-treated group, animals received saline (10 ml/kg) instead of morphine (50 mg/kg) during the induction session. The antinociceptive effect of various doses of VGB alone was evaluated at different time set intervals (15, 30, 60 and 90 min) after single injection of VGB (5, 10 or 20 mg/kg; i.p.) as well.

2.6. Statistics

The results obtained are expressed as mean ± SEM (standard error of mean). The mean of %MPEs in all groups was subjected to two-way ANOVA followed by protected Bonferroni's test for multiple

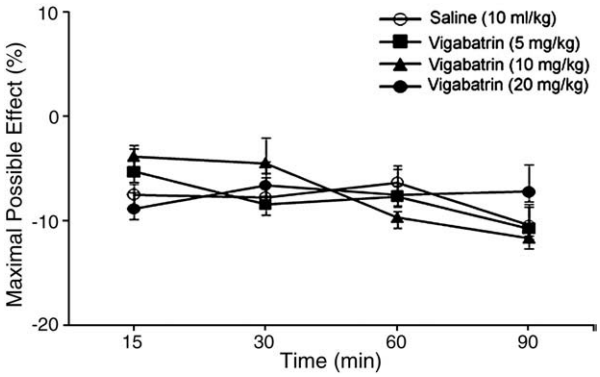

Fig. 2. The antinociceptive effects of different doses of vigabatrin (VGB) on percent of maximal possible effect (%MPE). Each point is the mean ± SEM for 7–8 mice.

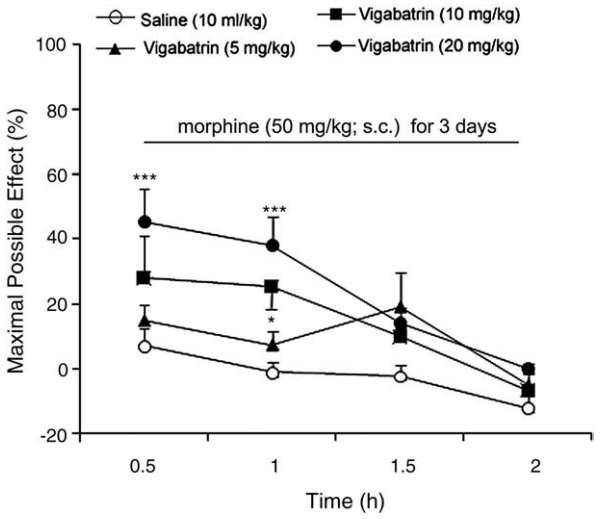

Fig. 3. The effect of different doses of vigabatrin on development of morphine tolerance. Animals received vigabatrin (5, 10 or 20 mg/kg; i.p.) or saline (10 ml/kg; i.p.), 30 min before morphine (50 mg/kg; s.c.) once daily for 3 days during the induction period. In day 4, the tail-flick latencies were tested at 30-min intervals after injection of challenge dose of morphine (5 mg/kg; s.c.). Each point is the mean ± SEM for 7–8 mice. *$P<0.05$, ***$P<0.001$ compared to the saline group.

comparisons between groups, as needed. *P*-values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Development of tolerance to morphine-induced antinociception

Two-way ANOVA followed by Bonferroni's test indicated that the antinociceptive response (the mean of %MPE values) to the challenge dose of morphine in day 4 decreased significantly in morphine-treated animals that received morphine daily during the induction period in comparison with the saline-treated group at most time set intervals [treatment main effect: $F(1,48)=56.2$, $P<0.0001$; time main effect: $F(3,48)=5.467$, $P=0.0026$; treatment × time interaction: $F(3,48)=3.719$, $P=0.0175$; Fig. 1]. Therefore, this result indicates that a tolerance phenomenon has been developed to morphine-associated antinociception after 3 days treatment. The total numbers of animals that reached the cut-off point (8 s) were 7 in pre-induction tests only.

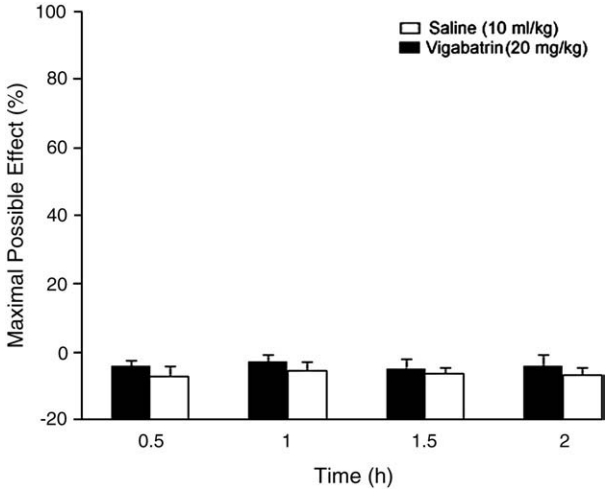

Fig. 4. Effect of the 3-day administration of vigabatrin or saline without injection of challenge dose of morphine on maximal possible effect (%MPE) values in comparison to those in saline control group at 30-min set intervals. Each point is the mean ± SEM for 7–8 mice.

3.2. Effects of different doses of VGB on tail-flick latency times

To evaluate the antinociceptive effect of VGB, tail-flick tests were done for each animal at 15, 30, 60 and 90 min after single injection of VGB (5, 10 or 20 mg/kg; i.p.). As shown in Fig. 2, two-way ANOVA indicated that there was no significant difference between analgesic effects (MPEs) of various doses of VGB alone when compared to those of the saline group [treatment main effect: $F(3,96)=0.1146$, $P=0.9513$; time main effect: $F(3,96)=3.127$, $P=0.0293$; treatment × time interaction: $F(9,96)=1.31$, $P=0.242$].

3.3. Effects of VGB on the development of morphine tolerance

Pretreatment of animals with VGB significantly reduced the development of tolerance to morphine antinociceptive effect in a dose dependent manner, as indicated by increment of %MPE in the VGB treatment groups. However, the lowest dose of VGB (5 mg/kg) had no effect on the development of morphine tolerance. Bonferroni's test indicated that in morphine-treated animals that received different doses of VGB (5, 10 or 20 mg/kg; i.p.) prior to morphine (50 mg/kg; s.c.) daily for 3 days during the induction period, the antinociceptive responses to the challenge dose of morphine in day 4

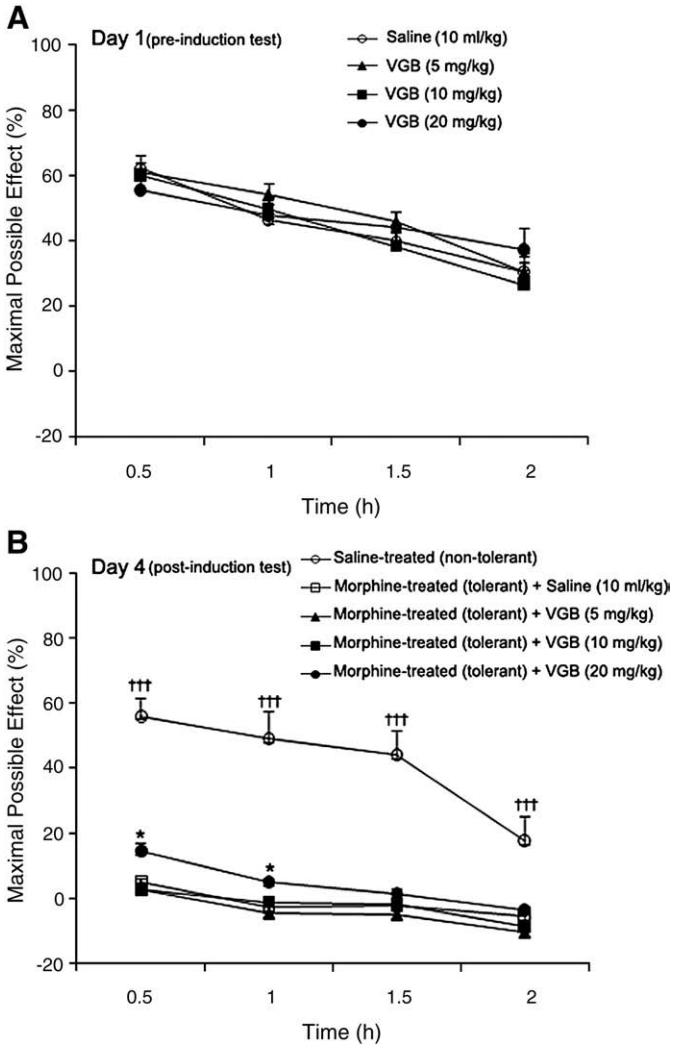

Fig. 5. The effect of different doses of vigabatrin on the expression of morphine-induced tolerance (A) prior to or (B) following 3 days of morphine tolerance induction (50 mg/kg; once daily). Various doses of vigabatrin or saline were administered 30 min prior to injection of challenge dose of morphine (5 mg/kg; s.c.) at day 1 (A) and day 4 (B). Each point is the mean ± SEM of percent of maximal possible effect (%MPE) for 7–8 mice. *$P<0.05$ compared to the saline-treated group. †††$P<0.001$ compared to morphine-treated control group.

significantly increased in comparison to the morphine (50 mg/kg; 3 days) alone treated group [treatment main effect: $F(3,96)=11.32$, $P<0.0001$; time main effect: $F(3,96)=15.32$, $P<0.0001$; treatment × time interaction: $F(9,96)=1.647$, $P=0.113$; Fig. 3]. Therefore, the highest dose of VGB (20 mg/kg) attenuated significantly the development of morphine tolerance.

On the other hand, administration of the high dose of VGB alone (20 mg/kg) for 3 days had no effect on tail-flick latency times in test day (day 4) without morphine challenge dose treatment as compared to those in the saline control group [treatment main effect: $F(1,48)=2.051$, $P=0.1586$; time main effect: $F(3,48)=0.1662$, $P=0.9187$; treatment × time interaction: $F(3,48)=0.02883$, $P=0.9933$; Fig. 4].

3.4. The effect of VGB on the expression of morphine tolerance

In this set of experiment, to evaluate the effect of different doses of VGB on expression of morphine tolerance, animals received VGB (5, 10 or 20 mg/kg, i.p.), 30 min prior to the challenge dose of morphine (5 mg/kg) before and after morphine-induced tolerance. Data analysis showed a significant difference between the saline-treated group (non-tolerant) and VGB-treated groups and even high dose (20 mg/kg) single injection of VGB could not inhibit the expression of tolerance to antinociceptive effect of morphine [treatment main effect: $F(1,48)=95.15$, $P<0.0001$; time main effect: $F(3,48)=1.055$, $P=0.3771$; treatment × time interaction: $F(3,48)=0.9252$, $P=0.4358$; Fig. 5]. Nevertheless, VGB at the dose of 20 mg/kg could significantly (approximately 10%) increase the %MPE at 0.5 and 1 h when compared to the morphine-treated group (tolerant).

4. Discussion

In this study we observed that (a) VGB decreased the development of morphine tolerance, (b) VGB could slightly inhibit expression of tolerance to the antinociceptive effect of morphine and (c) VGB alone has no antinociceptive effect in the tail-flick test as an acute pain model. The development of tolerance to analgesic effect of morphine, as demonstrated by the decreased antinociception of the challenge doses of morphine in animals, is a common medical problem which limits its efficacy and so prescription for long-term therapy. While it is unlikely that the analgesic efficacy of any currently available anticonvulsant drugs to be sufficient to eliminate the need for postoperative opioids, anticonvulsants may like non-steroidal anti-inflammatory drugs (NSAIDs), exert an opioid sparing effect (Gilron, 2006). Anticonvulsant agents are commonly used to treat neuropathic pain conditions because of their effects on voltage- and ligand-gated channels in central pain pathways. However, their interaction with ion channels in peripheral pain pathways is poorly understood. Gilron (2006) suggests that anticonvulsant drugs might decrease opioid consumption by either enhancing opioid analgesia or suppressing mechanisms of opioid tolerance.

Our data showed that VGB pretreatment could inhibit the development of morphine tolerance, dose-dependently. Other studies also revealed that most anticonvulsants such as gabapentin (Dirks et al., 2002; Gilron et al., 2003; Gilron et al., 2005; Hansen et al., 2004), lamotrigine (Arguelles et al., 2002), topiramate (Zullino et al., 2002), carbamazepine (Zullino et al., 2004), valproic acid (Tamayo and Contreras, 1983) and felbamate (Kosten et al., 1995) suppress opioid tolerance.

It has been shown that VGB in combination with morphine markedly increased both the peak effect and the duration of morphine-induced analgesia (Alvez et al., 1999; Sawynok and Labella, 1982). Furthermore, previous studies have shown that gabapentin has a synergistic effect with morphine analgesia (Meymandi et al., 2006). Phenytoin treatment also reduces opioid requirements (Yajnik et al., 1992). Our present study showed that different doses of VGB alone did not show any analgesic effect in the tail-flick test in mice. These findings rule out the involvement of VGB-induced antinociception in tolerance prevention. In contrast, Gilron (2006) has reported the analgesic effect of VGB in formalin test. Alvez et al. (1999) have also reported a possible dose dependent analgesic effect of VGB against noxious thermal stimulus of hindpaw in the rat.

In the present study, VGB had no significant additive effect on morphine's antinociception, and the highest dose of VGB could slightly attenuate the expression of tolerance. On the other hand, opioid tolerance is a complex phenomenon that involves one or more of several purposed mechanisms, including opioid receptor downregulation, alterations in binding of the peptide to the receptor, modulation of the G-protein-coupled receptor activation, alterations of downstream receptor processes, and possible changes in drug disposition to the receptor site (Liu and Anand, 2001; Taylor and Fleming, 2001). While the intricacies of this process have yet to be elucidated, the data presented herein suggest a major role of GABAergic in modulating loss of antinociceptive effect during prolonged morphine administration. In conclusion, our results indicate that VGB alone has no antinociceptive effect while it can prevent the development but lesser the expression of morphine tolerance in mice. Therefore, to inhibit the tolerance, the presence of VGB during development of tolerance to the morphine's analgesia is indispensable.

Acknowledgement

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References

Abdulrazzaq YM, Padmanabhan R, Bastaki S, Ibrahim A, Nurulain M, Shafiullah M. Effect of maternal administration of vigabatrin during late gestation on fetoplacental amino acid profile in the mouse. Reprod Toxicol 2005;20:549–60.
Alvez DA, Castro-Costa C, Charvalho A, Santos F, Silveira D. Possible analgesic effect of vigabatrin in animal experimental chronic neuropathic pain. Arq Neuropsiquiatr 1999;57:916–20.
Arguelles CF, Torres-Lopez JE, Granados-Soto V. Peripheral antinociceptive action of morphine and the synergistic interaction with lamotrigine. Anesthesiology 2002;96:921–5.
Bie B, Pan ZZ. Increased glutamate synaptic transmission in the nucleus raphe magnus neurons from morphine-tolerant rats. Mol Pain 2005;1:7.
Brodner RA, Taub A. Chronic pain exacerbated by long-term narcotic use in patients with non-malignant disease: clinical syndrome and treatment. Mt Sinai J Med 1978;45:233–7.
Czuczwar M, Kis J, Swiader M, Turski WA, Przesmycki K. Evaluation of interaction between valproate and baclofen in the formalin test in mice. J Pharmacol 2001;53:51–4.
D'amour FE, Smith DL. A method for determining loss of pain sensation. J Pharmacol Exp Ther 1941;72:74–9.
Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97:560–4.
Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Anesth Analg 2000;91:185–91.
Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin. JAMA 2005;293:3043–52.
Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. Br Med J 1997;314:180–1.
Gilron I. The role of anticonvulsant drugs in postoperative pain management: a bench-to-bed-side perspective. Can J Anesth 2006;53:562–71.
Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin or their combination for neuropathic pain. N Engl MED 2005;352:1324–34.
Gilron I, Biederman J, Jhamandas K, Hong M. Gabapentin blocks and reverses antinociceptive morphine tolerance in the rat paw-pressure and tail-flick tests. Anesthesiology 2003;98:1288–92.
Gram L, Larsson OM, Johnsen AH, Schousboe A. Effects of valproate, vigabatrin and aminooxyacetic acid on release of endogenous and exogenous GABA from cultured neurons. Epilepsy Res 1988;2:87–95.
Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman Gilman's the pharmacological basis of therapeutics. New York: McGraw Hill; 2001. p. 569–619.
Hansen C, Gilron I, Hong M. The effects of intrathecal gabapentin on spinal morphine tolerance in the rat tail-flick and paw pressure tests. Anesth Analg 2004;99:1180–4.
Haghparast A, Khani A, Lashgari R, Fallahian S. Reducing the time and dose of morphine application used in Marshall and Grahame-Smith method for induction of morphine tolerance and dependence in mice. Drug Alcohol Depend 2008a;93:185–9.
Haghparast A, Khani A, Naderi N, Alizadeh AM, Motamedi F. Repeated administration of nicotine attenuates the development of morphine tolerance and dependence in mice. Pharmacol Biochem Behav 2008b;88:385–92.

Jhamandas K, Powell KJ, Quirion R, Milne B. Opioid tolerance and physical dependence: role of spinal neuropeptides, excitatory amino acids and their messengers. Pain Res Manag 2000;5:25–32.
Kosten TA, DeCaprio JL, Rosen MI. The severity of naloxone-precipitated opiate withdrawal is attenuated by felbamate, a possible glycine antagonist. Neuropsychopharmachology 1995;13:23–33.
Liu J, Anand KJS. Protein kinases modulate the cellular adaptations associated with opioid tolerance and dependence. Brain Res Rev 2001;38:1-19.
Matthews EA, Dickenson AH. A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy. Anesthesiology 2002;96:633–40.
Meymandi MS, Sepehri GR, Mobasher M. Gabapentin enhances the analgesic response to morphine in acute model of pain in male rats. Pharmacol Biochem Behav 2006;85: 185–9.
Nestler EJ. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. Trends Pharmacol Sci 2004;25:210–8.
Orii R, Ohashi Y, Halder S, Giombini M, Maze M, Fujinaga M. GABAergic interneurons at supraspinal and spinal levels differently modulate the antinociceptive effect of nitrous oxide in Fischer rats. Anesthesiology 2003;98:1223–30.
Powell KJ, Hosokawa A, Bell A, Sutak M, Milne B, Quirion R, et al. Comparative effects of cyclo-oxygenase and nitric oxide synthase inhibition on the development and reversal of spinal opioid tolerance. Br J Pharmacol 1999;127:631–44.
Sawynok J, LaBella FS. On the involvement of GABA in the analgesia produced by baclofen, muscimol and morphine. Neuropharmacology 1982;21:397–403.
Shimoyama M, Shimoyama N, Inturrisi CE, Elliott KJ. Gabapentin enhances the antinociceptive effects of spinal morphine in the rat tail-flick test. Pain 1997;72: 375–82.
Tamayo L, Contreras E. A dual action of valproic acid upon morphine analgesia and morphine withdrawal. Pharmacology 1983;26:297–302.
Taylor DA, Fleming WW. Unifying perspectives in the mechanisms underlying the development of tolerance and physical dependence to opioids. J Pharmacol Exp Ther 2001;297:11–8.
Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004;110:221–31.
Woolf CJ, Chong MS. Preemptive analgesia: treating postoperative pain by preventing the established of central sensitization. Anesth Analg 1993;77:362–79.
Yajnik S, Singh GP, Kumar M. Phenytoin as a coanalgesic in cancer pain. J Pain Symptom Manage 1992;7:209–13.
Zarrindast MR, Dinkub Z, Homayoun H, Bakhtiarian A. Dopamine receptor mechanisms and morphine tolerance in mice. J Pysychopharmachol 2002;16:261–6.
Zullino DF, Cottier AC, Besson J. Topiramate in opiate withdrawal. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:1221–3.
Zullino DF, Krenz S, Favrat B, Zimmermann G, Bertschy G, Besson J. The efficiency of a carbamazepine–mianserin combination scheme in opiate detoxification. Hum Psychopharmacol 2004;19:425–30.