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ORIGINAL INVESTIGATION

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Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference

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Abstract *Rationale*: Psychological dependence to the opioid analgesic morphine is attributable to the rewarding properties of the drug, and its evolution can be divided into two distinct phases: development and maintenance. Both phases can be studied using conditioned place preference (CPP). *Objectives*: To determine whether the two phases can be influenced by pre-treatment with gabapentin-like compounds. *Methods*: CPP to morphine was used to demonstrate the rewarding properties of morphine in the presence or absence of gabapentin-like compounds. In-vivo microdialysis in the nucleus accumbens was used to determine the effects of gabapentin or pregabalin on morphine-induced dopamine release. *Results*: Pretreatment with either gabapentin (10–100 mg/kg p.o.) or pregabalin (3–30 mg/kg p.o.) attenuated CPP induced by a submaximal dose of morphine (0.75 mg/kg). Neither gabapentin nor pregabalin had any effect alone in the CPP test. Both gabapentin-like compounds blocked the effect of morphine (0.75 mg/kg s.c.) to increase the release of dopamine in the nucleus accumbens. Studies of the maintenance of CPP to morphine showed CPP was maintained for at least 4 days after the initial test. In a second experiment, it was found that pregabalin (injected once, 24 h after CPP had been demonstrated) was able to reverse morphine-induced CPP. *Conclusions*: Neither gabapentin nor pregabalin induced CPP, but both compounds blocked the development of CPP to morphine and also blocked morphine's effects on dopamine release. Furthermore, pregabalin blocked the maintenance of morphine-induced CPP. It is concluded that gabapentin-like compounds, which have no intrinsic rewarding properties, may have some therapeutic use in the treatment of opioid dependence.

Keywords Gabapentin-like compounds · Morphine · Conditioned place preference

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Introduction

Morphine and related opioids are widely used in the clinic for their potent analgesic effects in the relief of moderate to severe pain. Their use, however, can be limited by the dependence liability of this class of drugs, which is due in no small part to their reinforcing properties. The production of the dependent state is coincident with the development of tolerance with chronic treatment and is associated with a physical withdrawal syndrome on abrupt cessation of treatment. Due to these limitations, it is of great importance to develop pharmacological treatments for pain for which there is little or no dependence liability.

One such class of compound that is receiving increasing attention in this context are the gabapentin-like compounds. The potential utility of gabapentin-like compounds for the relief of pain has been suggested by the findings from a number of pre-clinical tests reporting antihyperalgesic or anti-allodynic effects (Field et al. 1997) and is now firmly supported by clinical experience (Backonja et al. 1998; Rowbotham et al. 1998). Although the mechanism of action has not yet been established, gabapentin and related compounds, including pregabalin (S(+)-3-isobutylgaba), are known to bind to the alpha-2-delta binding site of voltage-gated calcium channels (Dissanayake et al. 1997). This binding site is distributed throughout the central nervous system (CNS; Hill et al. 1993) and is present at high density in the superficial laminae of the dorsal horn of the spinal cord (Philp et al. 1999) where gabapentin is believed to act in producing its antihyperalgesic effects (Field et al. 1997; Shimoyama et al. 1998).

Recently, it has been reported that the antinociceptive effects of gabapentin and morphine synergise when the two are given in combination (Shimoyama et al. 1998). Given the possibility that the two classes of drug may be used as a co-therapy for analgesia, it is important to consider whether some form of synergy may extend to the rewarding properties of the opioids. In an experimental context, this may be addressed by posing the question whether treatment with a gabapentin-like compound affects the development of place preference to morphine.

The process by which dependence to drugs of abuse occurs has some basis in the rewarding or reinforcing properties of the drugs and can be thought of as taking two distinct phases: development and maintenance. The conditioned place preference (CPP) test can be used to study these processes. Rats are trained to associate one side of a two-compartment chamber with vehicle and the other side with the drug of study (Schechter and Calcagnetti 1993). On the test day, rats are placed in the apparatus (untreated) and allowed freedom to explore; animals that show place preferences spend significantly more time in the drug-paired side than in the saline-paired side. This test has been used to demonstrate the reinforcing properties of a number of classes of compound and is particularly powerful where μ-opioid agonists, such as morphine, are concerned (Phillips and LePiane 1980; Mucha et al. 1982).

In the present study, the first series of experiments examined the reinforcing effects of gabapentin and pregabalin alone and in conjunction with morphine, using the CPP test in the rat. In parallel, the effects of gabapentin or pregabalin were tested on the increase by morphine of release of dopamine in the nucleus accumbens. The importance of the contribution of this response to the rewarding properties of opiates has been long accepted (Spyraki et al. 1983), much as the role of the mesocorticolimbic system in reinforcement and reward generally is considered to be well established (Leshner and Koob 1999). In a final set of experiments, we investigated whether pregabalin could also attenuate an already established place preference, i.e. prevent maintenance. Such a property could point to a potential utility for gabapentin-like compounds against established opioid addiction.

Materials and methods

Animals

Male, hooded Lister rats (250–300 g at the beginning of the experiment) were used for CPP and in-vivo microdialysis studies. Rats were housed in groups of six for at least 1 week for behavioural experiments or groups of five for 2 weeks for microdialysis experiments, following delivery from the supplier (Charles River, Margate, UK). Rats for CPP studies were housed in the testing room with lights on from 0700 hours to 1900 hours. During this period, lights were dimmed (approximately 50 lux) between 0900 hours and 1700 hours. Rats for microdialysis experiments were housed in a holding room with lights on from 0700 hours to 1900 hours. All animals received food and water ad libitum, and the temperature (20°C) and humidity (60%) were kept constant.

All experiments were conducted according to the standards laid down by the Home Office Scientific Animals Procedures Act 1986 and under the jurisdiction of Project Licences PPL 770 1177 and PPL 770 1264.

Apparatus

Each animal was tested in one of six boxes constructed of Perspex, consisting of two compartments identical in size (34×25×32 cm). The compartments were joined by a tunnel (4×10×8 cm) that could be closed at both ends by guillotine doors coloured to match the facing compartment. The two compartments differed in colour and tactile cues: one was painted white and had a colourless rough pyramid Perspex floor; the other was painted grey and had a smooth floor. Translucent Perspex lids were used to cover each compartment during conditioning periods. The CPP apparatus was dimly lit during conditioning and test days using red lights situated above the compartments.

Conditioned place preference

CPP involved two phases: conditioning and testing. In the conditioning phase, animals were given conditioning sessions with drug treatment paired with one compartment for one session and saline vehicle (1 ml/kg) paired with the other compartment in the following session. Sessions were separated by 5 h to allow for elimination of drugs. A control group of rats was administered saline on both training sessions. Drug or saline was administered immediately preceding placement in the given compartment. On conditioning days, the entrances to the tunnel were blocked. Rats were given eight training sessions (two per day), each conditioning session lasting 45 min. All treatment groups were counterbalanced such that half of each group received training in one side of the apparatus and half in the other side. The boxes were washed with a diluted solution of detergent between each group of subjects to mask any odours left from previous rats. In the testing phase, rats were not administered with any substance but were allowed free access to both compartments through the dividing tunnel. Test sessions were carried out on the fifth day of the experiment and were of 900 s (15 min) duration. The groups were tested in a counterbalanced order so that half of those trained to associate the drug with the grey side were placed in the grey side at the beginning of the test; the others were placed in the white side. Likewise, half of those trained in the white side were placed in the white side at the beginning of the test and half in the grey side. The time spent in each compartment was recorded using solid state equipment (Coulbourn Instruments) and the 'preference' score was calculated for each rat from the total time (s) spent in the assigned drug compartment minus total time (s) spent in the saline compartment (D–S).

Development of place preference

Initially, the effects of morphine (0.1–3 mg/kg s.c.; n=6–15 per group), gabapentin (10, 30 and 100 mg/kg p.o.; n=9 per group) and pregabalin (3, 10 and 30 mg/kg p.o.; n=9 per group) alone on place preference were determined. Thus, animals were trained and tested to associate gabapentin, pregabalin or morphine with one compartment and saline with the other compartment. To determine the effect of gabapentin-like compounds on the development of morphine-induced CPP, two separate experiments were performed. Subjects were separated into groups that received (a) saline (1 ml/kg p.o.) or gabapentin (30 mg/kg and 100 mg/kg p.o.; n=18 per group), or (b) saline (1 ml/kg, p.o.) or pregabalin (1, 3, 10 or 30 mg/kg p.o.; n=9–15 per group). Morphine (0.75 mg/kg s.c.) was administered to all animals immediately before they were placed in the boxes, 60 min after administration of the gabapentin-like compounds. These groups were conditioned and tested as previously described.

Maintenance

Rats were trained as above in order to establish a CPP to morphine at a dose of 0.75 mg/kg, over a period of eight conditioning sessions. Subjects were then tested on day 5 for evidence of a CPP. Those rats showing at least 100 s of CPP were then allocated to one of two groups. On day 6, half of the rats (group 1; *n*=10) were administered saline (1 ml/kg p.o., 60 min prior to testing) and the other half (group 2; *n*=10) were given pregabalin (10 mg/kg p.o., 60 min before testing). On day 7 and day 8, rats were tested again; however, they received no treatment prior to testing.

In-vivo microdialysis

Surgery

Stereotaxic co-ordinates were verified histologically according to Paxinos and Watson (1986). Rats were anaesthetised via inhalation of 3% isoflurane (Abbott Laboratories, UK) in oxygen and positioned in a stereotaxic frame (Kopf Instruments). The skull was exposed and the incisor bar adjusted for each rat such that bregma and lambda were at the same height. Three indentations were made in the skull to accommodate screws that, together with the application of dental cement, held the cannulae in place. For cannulation of the nucleus accumbens, a BAS intracerebral guide cannula was implanted at a point 1.7 mm anterior of bregma, 0.15 mm lateral of the midline and 0.61 mm below the level of the dura. A microdialysis probe [BAS (UK) Ltd.] was then implanted down the guide cannula and secured such that the active portion of the membrane (2-mm long) extended into the nucleus accumbens. While the animal recovered from surgery in the test chamber, the probe was connected via polyethylene tubing (protected by a metal tether connected to a swivel hooked onto a balance arm) to a Harvard precision pump and perfused overnight at 1 µl/min with artificial cerebrospinal fluid (aCSF) consisting of 140 mM NaCl, 1.2 mM $CaCl_2$, 4 mM KCl, glucose 11 mM, pH 7.0.

Testing

Approximately 18 h after surgery, dialysate samples were collected every 20 min and analysed for dopamine content using high pressure liquid chromatography (HPLC) with electrochemical detection. The system comprised a Severn Analytical solvent delivery pump and a Decade (Antec) detector with the analytical cell set at 750 mV. Dialysates were injected by partial loop filling onto a Hypersil C18 reverse-phase column (5 µm, 150 mm×4.6 mm) and eluted isocratically in 0.1 M NaH_2PO_4/0.05 mM NaEDTA/0.5 mM 1-octanesulfonic acid in 10% aqueous methanol (pH 5.4) at 0.9 ml/min. Fresh standard concentrations of dopamine were prepared daily for peak verification. Once a stable baseline level of dopamine was established (at least three consecutive samples), the rat was injected systemically (s.c.) with either vehicle (0.9% saline; *n*=8), morphine (0.75 mg/kg; *n*=15), pregabalin (10 mg/kg; *n*=8), morphine + gabapentin (30 mg/kg or 100 mg/kg; *n*=6 and 7, respectively) or morphine + pregabalin (*n*=8), and samples were collected for a further 3–4 h. Rats receiving either gabapentin or pregabalin prior to morphine were injected 40 min prior to injection with morphine. A final experiment addressed whether local application of pregabalin to the accumbens was able to influence the effects of s.c. morphine on extracellular dopamine levels in the accumbens. To do this, a stable baseline was achieved (as above) and then the normal aCSF perfusing through the probe was replaced with aCSF containing pregabalin (30 µM). Forty minutes later, morphine (0.75 mg/kg s.c.) was administered, with pregabalin remaining in the aCSF throughout the remainder of the collection period. Preliminary experiments showed that pregabalin does not elute at the same time as dopamine under the chromatographic conditions employed in these experiments.

Drugs and chemicals

Morphine sulphate (Sigma, UK), gabapentin and pregabalin (both prepared in-house at Pfizer Global R&D, UK) were dissolved in 0.9% saline and administered either s.c. or orally by gavage at the appropriate doses in a 1 ml/kg volume. All solvents and reagents for the mobile phase used for HPLC were obtained from Fisher Scientific (Leicester, UK).

Data analysis

For CPP experiments, total time spent in the drug-paired compartment (D) and total time spent in saline-paired compartment (S) were compared using Wilcoxon's tests for matched pairs. For microdialysis experiments, levels of dopamine were expressed as percentage of basal [mean of three samples taken (i) 20 min before injection and (ii) 20 min and (iii) 40 min after injection]. Data were then analysed for group differences using multifactor repeated-measures analysis of variance (ANOVA) followed by Sidak's post-hoc tests with drug treatment and time as factors. Single-factor ANOVA with post-hoc Dunnett's test was used to determine within-group drug effects across time.

Results

Studies on development of place preference to morphine

Dose response to morphine

Morphine was found to induce a dose-related increase in the level of preference expressed towards the drug-paired side of the apparatus that was significant at 0.3, 1, 2 and 3 mg/kg. At the highest dose tested, 3 mg/kg, the effect was lower than that at 2 mg/kg (Fig. 1). This may have been due to either sedation or the beginnings of a place aversion. From this initial experiment, 0.75 mg/kg was selected as a submaximal dose of morphine with

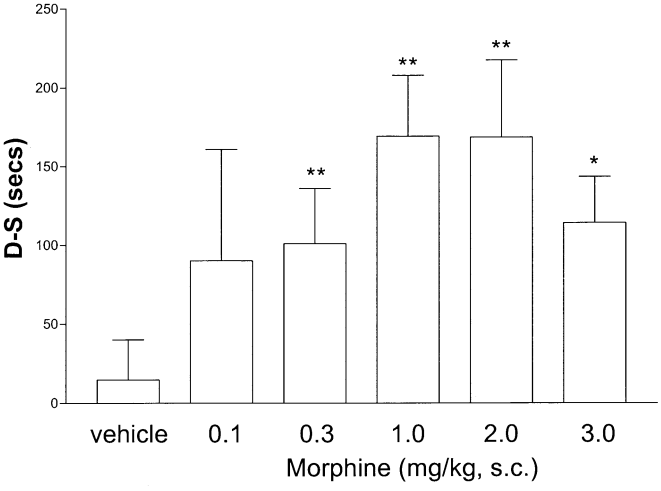

Fig. 1 Mean±SEM (s) time spent in the drug-paired side minus the time spent in the saline-paired side of the place preference boxes. Data show the effect of increasing concentrations of morphine on the level of preference to the drug-paired side. **P*<0.05, ***P*<0.01 Wilcoxon's matched pairs test, drug-paired side vs saline-paired side

Table 1 Mean±SEM (s) of drug-paired side minus saline-paired side (D–S). Data show the response to increasing doses of gabapentin and pregabalin

Treatment	D–S (s)
Gabapentin (mg/kg p.o.)	
Vehicle (0)	–21.7±55.9
10	6.2±55.9
30	–20.6±42.4
100	38.8±52.2
Pregabalin (mg/kg p.o.)	
Vehicle (0)	40.9±58.7
3	–35.8±55.9
10	21.8±41.0
30	–31.6±60.9

which to perform the interaction studies with gabapentin and pregabalin.

Effect of gabapentin and pregabalin on development of place preference to morphine

Neither gabapentin nor pregabalin when administered alone to rats had any significant effect on the level of bias to either side of the apparatus (Table 1).

In a second set of experiments, rats were trained to associate morphine or morphine after pretreatment with gabapentin (30 mg/kg or 100 mg/kg) or pregabalin (1–30 mg/kg p.o.) with one side of the apparatus and saline with the other side. It was found that the animals receiving morphine alone showed a significant place preference ($P<0.01$), as did animals receiving morphine after gabapentin at 30 mg/kg or pregabalin at 3 mg/kg. However, place preference was attenuated by pretreatment with gabapentin at the 100 mg/kg dose or with pregabalin at 10 mg/kg (Fig. 2). For reasons unknown, pregabalin at 30 mg/kg failed to attenuate the place preference.

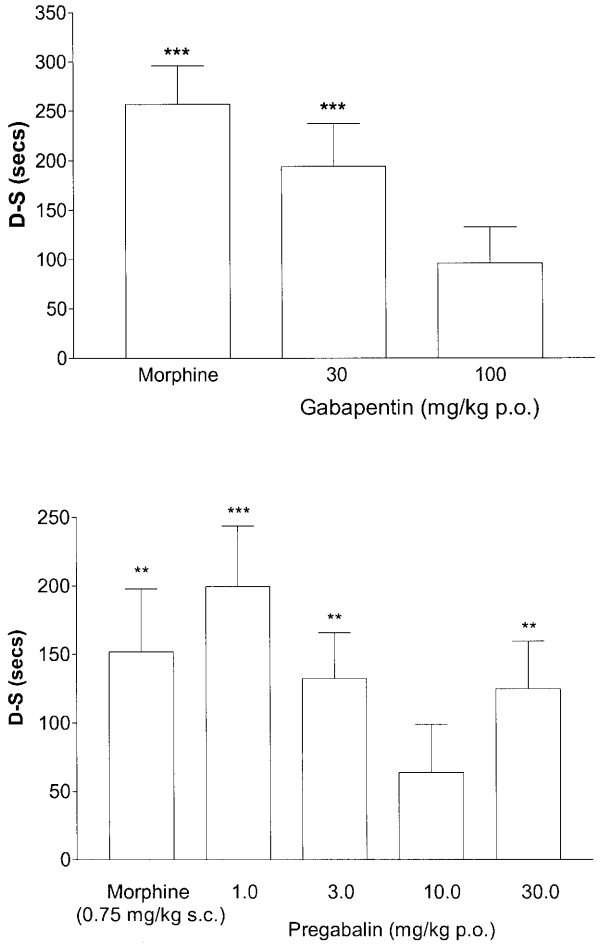

Fig. 2 Mean±SEM (s) time spent in the drug-paired side minus the time spent in the saline-paired side of the place preference boxes. Data show the effect of either gabapentin (*upper panel*) or pregabalin (*lower panel*) pretreatment on the level of place preference to a submaximal dose of morphine (0.75 mg/kg s.c.). $^{**}P<0.01$, $^{***}P<0.001$ Wilcoxon's matched pairs test, drug-paired side vs saline-paired side

Effect of systemically administered gabapentin and pregabalin on morphine-induced increases in extracellular dopamine levels in the nucleus accumbens of the freely moving rat

Gabapentin

Statistical analysis using multifactor ANOVA with repeated measures showed a significant effect of drug treatment ($F_{3,30}=6.1$, $P<0.01$) and a significant effect of time ($F_{12,360}=5.1$, $P<0.01$). A significant drug × time interaction ($F_{36,360}=2.4$, $P<0.01$) indicated that the effect across time was influenced by particular drug treatments, and post-hoc Sidak's tests showed significant differences between treatments at distinct time points (Fig. 3, left hand panel). Post-hoc Dunnett's tests (compared with $t=20$ min) following single-factor ANOVA showed significant increases ($P<0.05$ at each point) in dopamine levels following morphine (80, 100, 120 and 140 min after injection) and morphine plus gabapentin 30 mg/kg (100, 120, 140 and 160 min after morphine injection) treatment. However, there was a complete blockade of the effect of morphine on dopamine levels following pretreatment with gabapentin at 100 mg/kg, and no significant differences were found.

Pregabalin

Multifactor ANOVA with repeated measures showed a significant effect of drug ($F_{3,33}=3.9$, $P<0.05$) and a significant effect of time ($F_{12,396}=4.0$, $P<0.01$) and a significant drug × time interaction ($F_{36,396}=1.6$, $P<0.05$). Significant differences between groups at distinct time points, identified using post-hoc Sidak's tests are shown on Fig. 3 (right hand panel). Dunnett's post-hoc tests (data points compared with t=20 min) following single-

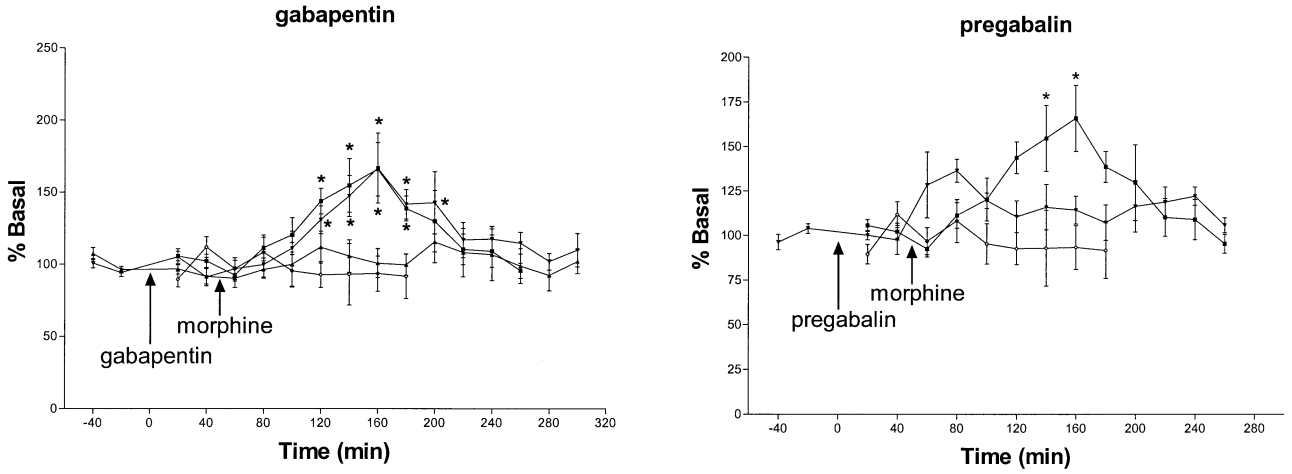

Fig. 3 Mean±SEM percentage basal dopamine levels in the nucleus accumbens of the freely moving rat. *Left hand panel* shows data from rats treated with either vehicle (o), morphine (0.75 mg/kg s.c.; ✝) or gabapentin [30 mg/kg (∇) or 100 mg/kg (Δ) s.c.] plus morphine. *Right hand panel* shows the effect of either vehicle (✝), morphine (0.75 mg/kg s.c.; ✝) or pregabalin (10 mg/kg s.c.) plus morphine (∇). *P<0.05 Sidak's post-hoc test vs vehicle following multifactor ANOVA with repeated measures

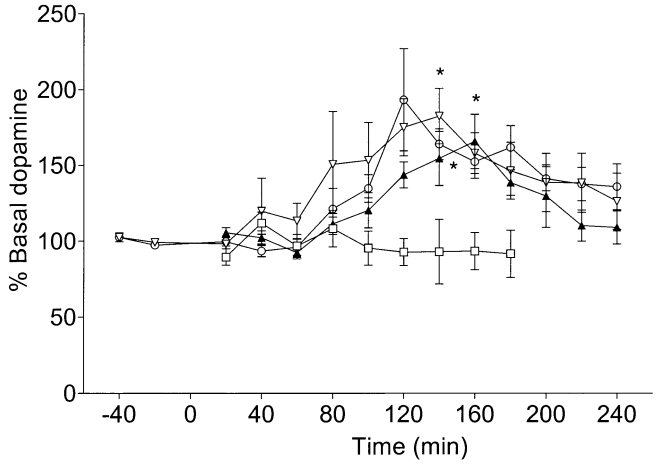

Fig. 4 Mean±SEM percentage basal dopamine levels in the nucleus accumbens of the freely moving rat following vehicle (✝), morphine (0.75 mg/kg s.c.; ✝) or pregabalin [30 μM (∇) or 100 μM (o)] plus morphine. *P<0.05 post-hoc Sidak's test vs vehicle following multifactor ANOVA with repeated measures

factor ANOVA showed significant increases (P<0.05 at each point) in dopamine levels 80, 100, 120 and 140 min following morphine administration but not following pregabalin (10 mg/kg) pretreatment.

Effect of local administration of pregabalin (30 μM) to the nucleus accumbens on morphine-induced increases in extracellular dopamine levels in the nucleus accumbens of the freely moving rat

Multifactor ANOVA with repeated measures showed a significant effect of drug ($F_{3,36}$=4.66, P<0.01), time ($F_{12,372}$=6.6, P<0.01) and a significant drug × time interaction ($F_{36,372}$=1.6, P<0.05). Significant differences between groups at distinct time points using Sidak's test are presented in Fig. 4. Post-hoc Dunnett's tests showed significant effects (P<0.05 at each point) of morphine and effects of pregabalin plus morphine at t=80, 100, 120 and 140 min demonstrating that pregabalin had no effect on the response to morphine.

Studies on the maintenance of place preference to morphine

Time course of CPP to morphine

Rats (n=36) were trained as before to establish a CPP to morphine and then, following testing, those animals showing at least 100 s of preference to the drug-paired side were allocated to one of four groups (n=7–8). Each group was then tested once on each of the following 4 days to establish how long the place preference was retained. As can be seen in Table 2, there was a significant place preference to morphine on each of the four days following the initial test.

Effect of pregabalin on maintenance of place preference to morphine

Place preference to morphine was established in a group of rats, and those showing at least 100 s of preference were allocated to one of two groups (n=10/group). On the day following the initial test, rats were then treated with either vehicle (group 1) or pregabalin (10 mg/kg p.o.; group 2) 60 min prior to testing for preference. It was found that, while group 1 still showed significant place preference (P<0.01), those treated with pregabalin (group 2) showed no place preference to morphine (Fig. 5). The animals were returned to the home cage and re-tested on each of the following 2 days with no further drug treatment. It was found that the place preference [while being maintained in group 1 (P<0.01 each time)] returned to the

Table 2 Mean±SEM (s) of drug-paired side minus saline-paired side. Data show the maintenance of conditioned place preference to morphine over a period of 96 h after the initial test

Time after initial test	24 h	48 h	72 h	96 h
Initial test score	206±26.7***	259.9±38.7***	267.1±40.4***	150.9±44.7**
Second test score	301.8±105.7***	150.3±87.1*	145.1±38.8***	194.4±100.2*

***P<0.001, **P<0.01, *P<0.05 Wilcoxon's test for matched pairs, drug-paired side vs saline-paired side

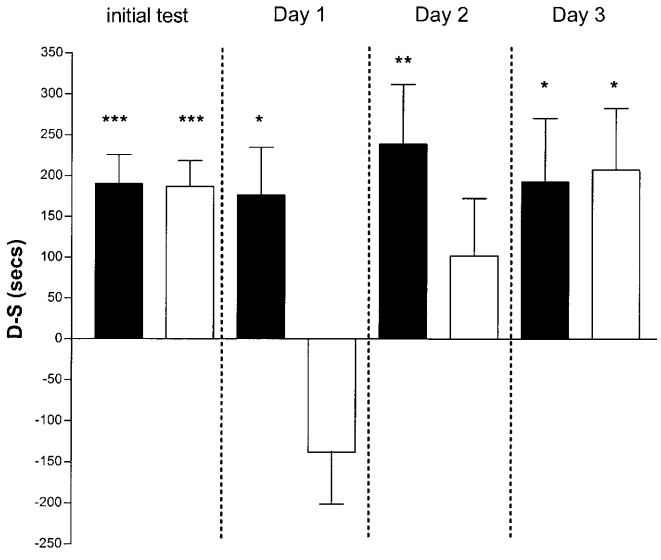

Fig. 5 Mean±SEM (s) time spent in the drug-paired side minus the time spent in the saline-paired side of the place preference boxes. Data show that pregabalin (10 mg/kg p.o., administered once, 1 h prior to testing, 24 h after the initial test) is able to reverse the established place preference to morphine (see Methods for description of experiment). ***P<0.001, **P<0.01, *P<0.05 Wilcoxon's tests for matched pairs drug paired side vs saline paired side

rats in group 2 (P<0.05) 48 h after pregabalin treatment, indicating the blockade of the established place preference was dependent on the presence of pregabalin.

Discussion

The results of this series of experiments show that the rewarding properties of morphine during the process of development may be prevented by pre-treatment with either gabapentin or pregabalin. Furthermore, pregabalin was able to reverse an already established place preference to morphine. The effects of the gabapentin-like compounds are considered to be selective, and not as a result of an impairment of motor co-ordination, since no effects on motor function have been reported at the doses found to be effective in these studies (Field et al. 1997). These results have important implications in terms of both opioid analgesia and opioid dependence, since it demonstrates that it may well be safe to co-administer an opioid and a gabapentin-like compound (in order to benefit from the synergy of pain relief that has been shown to occur; Shimoyama et al. 1998) without the danger of enhanced dependence liability. These results also show that it may be possible to reduce the rewarding properties of opioids that may lead to dependence following chronic opioid administration. Under the present conditions, we are unable to address whether the gabapentin-like compounds are modifying the environmental cue per se. However, it does seem clear that pretreatment with a gabapentin-like compound induces a dissociation of the above-noted environmental cue from morphine since there is an attenuation of CPP to morphine in those animals receiving both compounds on the training days (irrespective of side of arena).

Classes of compounds that are commonly abused, e.g. opioids, have in common the property of increasing dopamine levels within areas of the mesolimbic system, such as the nucleus accumbens which is innervated by ascending neurones originating in the ventral tegmental area. It was found in the experiments reported here that morphine, at behaviourally relevant doses, increased dopamine levels in the nucleus accumbens. The increases in dopamine could be prevented by the prior systemic administration of either gabapentin or pregabalin at a dose that had been found to block the development of place preference. Opiate-induced increases in dopaminergic activity in mesolimbic regions are thought to lead to increased mood and motivation (Wise 1989) which in turn induces reinforcement and eventual dependence characterised by tolerance (requiring larger doses to surmount the loss of efficacy) and a withdrawal syndrome following elimination of the drug from the plasma. By blocking the increase in dopamine with either gabapentin or pregabalin pretreatment each time morphine was administered, reinforcement was prevented. However, it is not clear from experiments reported here how pregabalin was able to block the maintenance of place preference, i.e. reverse an already established place preference to morphine. While the development of place preference lends itself easily to microdialysis to study mechanisms of intervention, maintenance is not so amenable. Some groups (DiCiano et al. 1998; Weiss et al. 2000; Gerasimov et al. 2001) have shown that it is possible to measure the changes in dopamine within the environment on which the conditioning is dependent, and this approach would add further weight to our findings.

From the present results, it is not possible to deduce the site of action of pregabalin in the brain, where the effects of morphine on inducing CPP or increasing accumbal dopamine can be blocked. However, it would seem from the lack of effect on morphine-induced dopamine release, with local perfusion with pregabalin by reverse dialysis in the nucleus accumbens, that the site of action is remote from the accumbal dopaminergic terminal field. The ventral tegmental area (VTA) is one area of

consideration as it is known that both alpha-2-delta (Hill et al. 1993) and μ opioid (McBride et al. 1998) sites are present here, and this area in particular is critical to the expression of CPP to morphine (Bozarth 1987). Interestingly, several groups have reported that local injection of morphine into the nucleus accumbens does not induce CPP (Olmstead and Franklin 1997; Schildein et al. 1998). So it seems that the nucleus accumbens is required for the expression of the CPP to morphine as a downstream dopaminergic relay to areas such as the ventral pallidum (Bardo 1998). Kelsey et al. (1989) showed that lesions of the nucleus accumbens prevented CPP to morphine but did not block the ability to recognise an environment, since context-specific tolerance to morphine was not impaired. With respect to the prevention of morphine-induced increases in dopamine levels in the accumbens, this could occur either from an action at the VTA or within the accumbens itself, possibly via an increase in γ-aminobutyric acid function (Taylor 1997).

In conclusion, the results of the experiments described in this report demonstrate that both gabapentin and pregabalin are able to prevent the development of CPP to morphine and the increase in dopamine in the nucleus accumbens resulting from acute morphine administration. In addition, pregabalin was shown to prevent the maintenance of CPP to morphine. The fact that these substances influenced the effect of morphine on dopamine release led us to conclude that the effect on preference conditioning was due to a disruption of the association between the place cues and the rewarding effects of morphine. However, further experiments will be necessary to rule out whether the gabapentin-like compounds affect preference conditioning by simply introducing new stimuli to the training or test situation. The data provide early indication that the combination of an opioid and a gabapentin-like compound will not synergistically enhance the rewarding effect of the opioid, even though synergism has been reported to occur between morphine and gabapentin with respect to the analgesic properties of the two compounds. Additionally, these results also indicate that gabapentin-like compounds may reverse an established propensity to seek opioids and may therefore be useful agents for the pharmacological treatment of dependence to such compounds.

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