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The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain

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Abstract

We have tested for anti-nociceptive effects of the anticonvulsant KCNQ channel opener, *N*-(2-amino-4-(4-fluorobenzylamino)-phenyl)carbamic acid ethyl ester (retigabine), in rat models of experimental pain. In the chronic constriction injury and spared nerve models of neuropathic pain, injection of retigabine (5 and 20 mg/kg, p.o.) significantly attenuated ($P<0.05$) mechanical hypersensitivity in response to pin prick stimulation of the injured hindpaw. In contrast, retigabine had no effect on mechanical hypersensitivity to von Frey stimulation of the injured hindpaw in either model. Cold sensitivity in response to ethyl chloride was only attenuated ($P<0.05$) in the chronic constriction injury model. In the formalin test, retigabine (20 mg/kg, p.o.) attenuated flinching behaviour in the second phase compared with vehicle ($P<0.05$), and this effect was completely reversed by the KCNQ channel blocker 10,10-bis(4-pyridinylmethyl)-9(10*H*)-anthracenone (XE-991; 3 mg/kg, i.p.). Neither retigabine nor XE-991 administration affected the latency to respond to noxious thermal stimulation of the tail in control animals. These results suggest that retigabine may prove to be effective in the treatment of neuropathic pain.

Keywords: Anticonvulsant; Chronic constriction injury; Formalin test; Neuropathic pain; Spared nerve injury; Tail flick

1. Introduction

Dynamic changes in the expression and function of ligand and voltage-gated ion channels can occur within dorsal root ganglion neurones in response to tissue injury (Eglen et al., 1999; Waxman, 1999). These contribute to the injury-induced activation of primary afferent fibres, which can induce a state of prolonged neuronal hyperexcitability within the dorsal horn of the spinal cord (Woolf and Salter, 2000), a state that is closely correlated with behavioural hypersensitivity to both noxious (hyperalgesia) and non-noxious (allodynia) stimulation.

Multiple voltage-gated K^+ channels have been identified within dorsal root ganglion neurones (Gold et al., 1996a). Recent studies have demonstrated dramatic reductions in voltage-gated K^+ currents and K^+ channel subunit expression within axotomised dorsal root ganglion neurones (Ishikawa et al., 1999) and in animal models of neuropathic pain (Rasband et al., 2001). One of these, the M-current, is a subthreshold voltage-gated K^+ current that serves to stabilise the membrane potential and control neuronal excitability (Brown and Yu, 2000). Functional studies associate the M-current to homo- or hetero-multimers of KCNQ (2–5) protein subunits (Jentsch, 2000). These form voltage-gated K^+ channels, which are widely distributed throughout the nervous system. The KCNQ2 and KCNQ3 subunits are mutated in a rare form of inherited epilepsy (Jentsch, 2000; Rogawski, 2000), suggesting that drugs which can increase M-channel function may prove effective in depressing sustained neuronal firing and in controlling seizure discharge.

Injury-induced pain behaviours in animal models of chronic pain and in humans with various chronic pain conditions can also be attenuated by anticonvulsant drugs (Hunter et al., 1997; Backonja, 2001). The anticonvulsant drug *N*-(2-amino-4-(4-fluorobenzylamino)-phenyl)carbamic acid ethyl ester (retigabine) has been shown to activate KCNQ channels expressed in mammalian cells (Rundfeldt and Netzer, 2000) and native M-currents in rat sympathetic neurones (Tatulian et al., 2001; Wickenden et al., 2001). Taken together, this suggests that retigabine may prove to have as yet undescribed therapeutic potential in the treatment of various chronic pain conditions. To address this issue, we have tested for anti-nociceptive effects of retigabine in rat models of nociceptive, persistent and chronic pain.

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2. Materials and methods

Male Sprague–Dawley rats (body weight, 180–450 g; Möllegaard, Denmark) were housed together in groups of three to four animals under standard conditions with unrestricted access to food and water. Rats were housed in the room in which the testing procedure was performed to try and minimise any stress response to novel environmental cues. All experiments were conducted according to the ethical guidelines for investigations of experimental pain in conscious animals (Zimmerman, 1983), and the procedures were approved by the Danish Committee for Experiments on Animals (Dyreforsøgstilsynet). All behavioural experiments were conducted by an experimenter blinded to drug treatments.

2.1. Nerve injury models

The chronic constriction injury (Bennett and Xie, 1988) and spared nerve injury (Decosterd and Woolf, 2000) models of neuropathic pain were used in the current study, both of which have been described in detail previously. All rats were anaesthetised with chloral hydrate (Merck, Germany; 80 mg/kg, i.p.), and the skin of the lateral left thigh was incised. In chronic constriction injury animals, four chromic gut ligatures (4/0) were tied 1–2 mm apart loosely around the nerve. In spared nerve injury animals, the sciatic nerve and its three terminal branches were exposed. The tibial and common peroneal nerves were tightly ligated with 4/0 silk, and 2–3 mm of the nerve distal to the ligation was removed. Any stretching or contact with the intact sural nerve was avoided. In all rats, the muscle and skin were closed in two layers with absorbable surgical suture, and the skin was sutured together with hidden stitches using 4/0 silk thread. Only animals that recovered completely with no behavioural deficits after surgery was completed were used for subsequent behavioural testing.

2.2. Behavioural testing of nerve-injured animals

All behavioural tests (Erichsen and Blackburn-Munro, 2002) were conducted on animals at least 1 week after surgery. During testing, the animals were placed on an elevated metal grid allowing stimulation of the plantar surface of the paw (lateral aspect in spared nerve injury animals), and the animals were allowed to adapt to their environment for at least 15 min. Stimulation of the injured hindpaw was then initiated in the following order: von Frey, pin prick and ethyl chloride stimulation, according to the apparent degree of stress associated with the stimulus. Animals were allowed to recover for 1–2 min between the testing procedures. After baseline responses had been obtained, animals were administered with retigabine (20 mg/kg, p.o.), and the time course of drug actions on nociceptive behaviours followed every 30 min for a further 3 h.

To test for the presence of mechanical allodynia, a set of von Frey monofilaments (Stoelting, USA) was applied in increasing force until the rat withdrew the hindpaw. The threshold was taken as the lowest force that caused at least three withdrawals out of five consecutive stimuli.

The pin prick test was used to test for the presence of mechanical hyperalgesia. The plantar surface of the hindpaw was touched with the point of a safety pin at an intensity insufficient to penetrate the skin. A cutoff time of 15 s was applied to long withdrawals often seen for the paw ipsilateral to the nerve injury.

To test for the presence of cold allodynia, ethyl chloride (Perstorps, Sweden) was sprayed onto the plantar surface of the hindpaw, and animals were observed for both the intensity of the response and any paw withdrawal duration. This was then classified according to the following scale: 0—no visible response (0 s duration); 1—startle response without paw withdrawal (0 s duration); 2—clear withdrawal of the paw (0.5–5 s duration); 3—prolonged withdrawal (5–30 s duration) often combined with flinching and licking of the paw; 4—prolonged repetitive withdrawal (>30 s duration) and/or vocalization.

2.3. Formalin test

Normal, uninjured animals were administered with retigabine (20 mg/kg, p.o.) and/or XE-991 (3 mg/kg, i.p.) at 30 and 5 min, respectively, before formalin injection, and these were habituated in separate testing cages before initiation of the formalin test. Formalin (5%, 50 μl, s.c.; formaldehyde solution, minimum 37%, diluted 1:20 in saline; Merck) was carefully injected into the plantar surface of the hindpaw using a 27-gauge needle. After administration, measurement of flinching behaviour was initiated. On the basis of the response pattern, two distinct phases (0–5 and 15–40 min) of nociceptive behaviour, characterised by flinching of the affected paw, were identified and scored (Blackburn-Munro et al., 2002).

2.4. Tail flick test

The reflex response to a noxious thermal stimulus was measured in normal, uninjured animals using the tail flick test (Ugo Basile, Comerio, Italy). A radiant heat source was focused on the underside of the tail 3 cm from its distal end. The apparatus was calibrated to give a tail flick latency of approximately 5–6 s (20 s automatic cutoff) before drug injection, enabling increases or decreases in tail flick latency to be measured to the nearest 0.1 s. Baseline measurements were made on the day before testing to familiarise the animals with the testing procedure. Two further baseline tail flick latency measurements were obtained before drug testing (two measurements at each timepoint separated by 5 min) to ensure that consistent reflex responses were present. Animals were then administered with retigabine (20 mg/kg, p.o.) and/or XE-991 (3 mg/kg, i.p.) at 30 and 5 min, respectively, before measurement of the tail flick latency response.

2.5. Rotarod testing for ataxia

In normal rats, changes in motor performance after retigabine administration were measured using the rotarod test (Erichsen and Blackburn-Munro, 2002). Rats were placed on the rotating rod at 4 rpm and were required to walk against the motion. The animals were acclimatised to the revolving drum by a training run the day before drug testing. They were placed on the drum for 2 min, and the number of times they fell was counted. Only animals that showed no impairment in motor coordination (determined to be present if any rat fell more than two times during the recording period) were included for subsequent testing. On the following day, after baseline responses had been established, animals were administered with retigabine (20 and 40 mg/kg, p.o.) before further testing 30 min later. The effective dose (ED_{50}) of retigabine required to induce ataxia was calculated as the dose that induced motor impairments in 50% of the animals.

2.6. Analysis

Analysis of the data was performed using Sigmastat 2.03. Data for all tests (except for cold stimulation) are presented as mean ± S.E.M. Unless stated otherwise, two-way repeated measures (RM) analysis of variance (ANOVA) was used to analyse the overall effects of the treatments, and for individual comparison, Bonferroni's *t*-test was applied. Data for cold stimulation are expressed as median ± median-derived absolute deviation (MAD). To analyse the overall effects, Friedman RM ANOVA on ranks was used followed by Mann–Whitney rank sum test for individual comparison. $P<0.05$ was considered to be statistically significant.

2.7. Drugs

The KCNQ opener *N*-(2-amino-4-(4-fluorobenzylamino)-phenyl)carbamic acid ethyl ester (D-23129; retigabine) and the KCNQ blocker 10,10-bis(4-pyridinylmethyl)-9(10*H*)-anthracenone (XE-991) (Zaczek et al., 1998; Wang et al., 2000) were synthesised at NeuroSearch. Retigabine and XE-991 were dissolved in 10% Tween 80. The pH of the final retigabine solution was between 2 and 3, and so, retigabine was given by oral administration in a volume of 5 ml/kg. XE-991 was administered intraperitoneally in a volume of 2 ml/kg.

3. Results

3.1. Effects of retigabine in nerve injury

In the chronic constriction injury and spared nerve injury models of neuropathic pain, pronounced mechanical allodynia (0.3 ± 0.7 and 0.4 ± 0.1 g, respectively), in response to von Frey hair stimulation of the ipsilateral hindpaw, was observed, compared with pre-surgery levels that typically ranged from 8.4 to 19.4 g. Both chronic constriction injury and spared nerve injury rats also showed marked mechanical hyperalgesia (10.6 ± 2.0 and 10.6 ± 0.8 s, respectively, compared with <0.5 s before surgery) and cold allodynia (2.5 ± 0.5 and 3.0 ± 0, respectively, compared with zero response before surgery) of the ipsilateral paw in response to noxious pin prick and ethyl chloride spray stimulation.

Administration of retigabine (5 and 20 mg/kg, p.o.) to chronic constriction injury rats had no effect on the withdrawal threshold in response to von Frey hair stimulation of the ipsilateral paw at any of the timepoints examined, compared with either the baseline withdrawal threshold (0.6 ± 0.4 and 0.2 ± 0.1 g, respectively) or with vehicle-treated animals (Fig. 1A). In contrast, pin prick stimulation of the ipsilateral hindpaw in chronic constriction injury rats was significantly attenuated by retigabine (5 mg/kg) to 2.6 ± 0.9 s ($P<0.05$ compared with baseline, two-way RM ANOVA) at 60 min (Fig. 1B). At the highest dose of retigabine tested (20 mg/kg) in chronic constriction injury animals, this attenuation was maintained until 120 min (4.6 ± 0.9 s, $P<0.05$ compared with baseline and corresponding vehicle treatment). Ethyl chloride stimulation of the ipsilateral hindpaw was also significantly attenuated by retigabine (20 mg/kg) from 30 min after injection compared with baseline (2 ± 0; $P<0.05$, Friedman RM ANOVA on ranks, Fig. 1C). This effect was maximal at 90 min (1 ± 0) and remained significantly attenuated until 120 min after injection of retigabine (both $P<0.05$).

Similarly, in the spared nerve injury rats, administration of retigabine (20 mg/kg, p.o.) had no effect on the withdrawal threshold in response to von Frey hair stimulation of the ipsilateral paw up to 180 min after administration, compared with either the baseline withdrawal threshold (0.3 ± 0.2 g) or with vehicle-treated animals (Fig. 2A). In contrast, pin prick stimulation of the lateral surface of the ipsilateral hindpaw was significantly reduced to 3.9 ± 1.6 s ($P<0.05$ compared with baseline), 60 min after administration of retigabine (Fig. 2B). The cold response after application of ethyl chloride to the ipsilateral hindpaw was unaffected by administration of retigabine for all timepoints examined, compared with either the baseline (3 ± 0) or corresponding vehicle (3 ± 0) cold responses (Fig. 2C).

3.2. Effects of retigabine and XE-991 in the formalin test

In rats administered with vehicle, subsequent injection of formalin resulted in a biphasic nociceptive response characterised by robust flinching of the affected hindpaw. Administration of either retigabine (20 mg/kg, p.o.) or XE-991 (3 mg/kg, i.p.) to rats, before injection of formalin, had no effect on flinching behaviour in the first phase of the test compared with rats administered with vehicle (Fig. 3A). In the second phase of the formalin test, the total

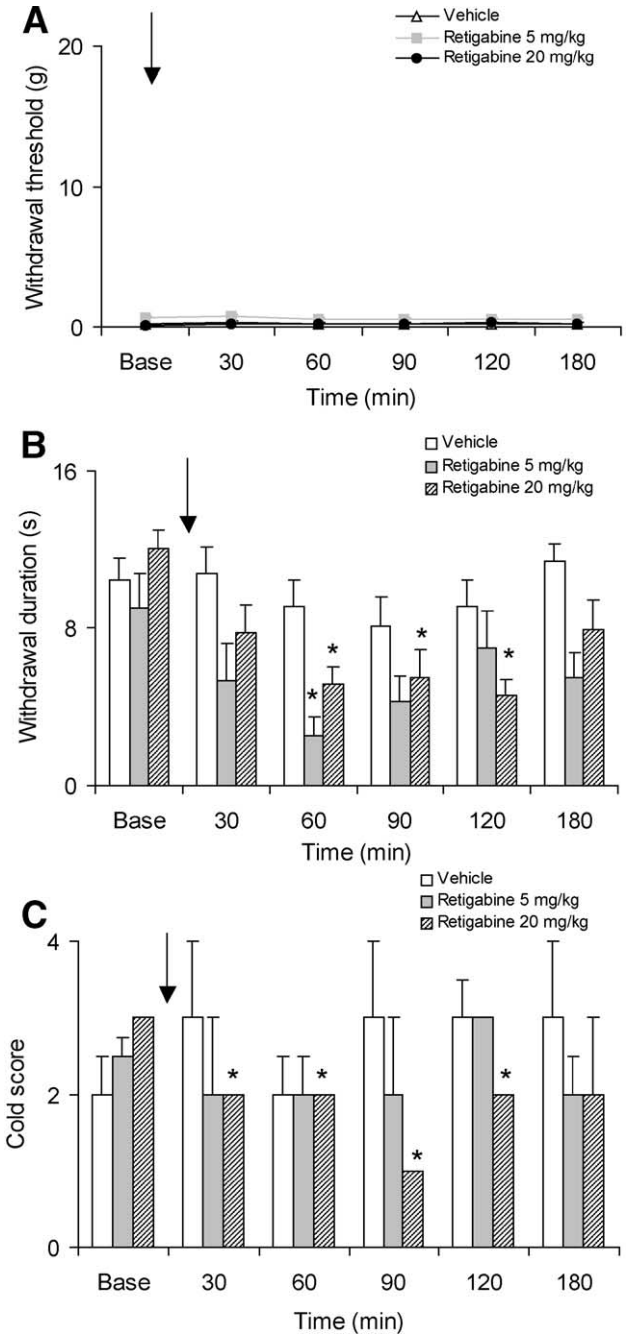

Fig. 1. Effects of retigabine on pain behaviours in chronic constriction injury rats. Retigabine (5 and 20 mg/kg, p.o.) was administered 30 min before testing for (A) mechanical allodynia in response to von Frey stimulation, (B) mechanical hyperalgesia in response to pin prick stimulation and (C) cold allodynia in response to ethyl chloride cold spray stimulation of the injured hindpaw. Retigabine had no effect on mechanical allodynia but did reduce mechanical hyperalgesia from $t = 60$ to 120 min and cold allodynia from $t = 30$ to 120 min, respectively. Data in (A) and (B) are presented as mean ± S.E.M. and in (C) as median ± MAD. *$P < 0.05$ vs. corresponding baseline. All groups $n = 7–13$ animals.

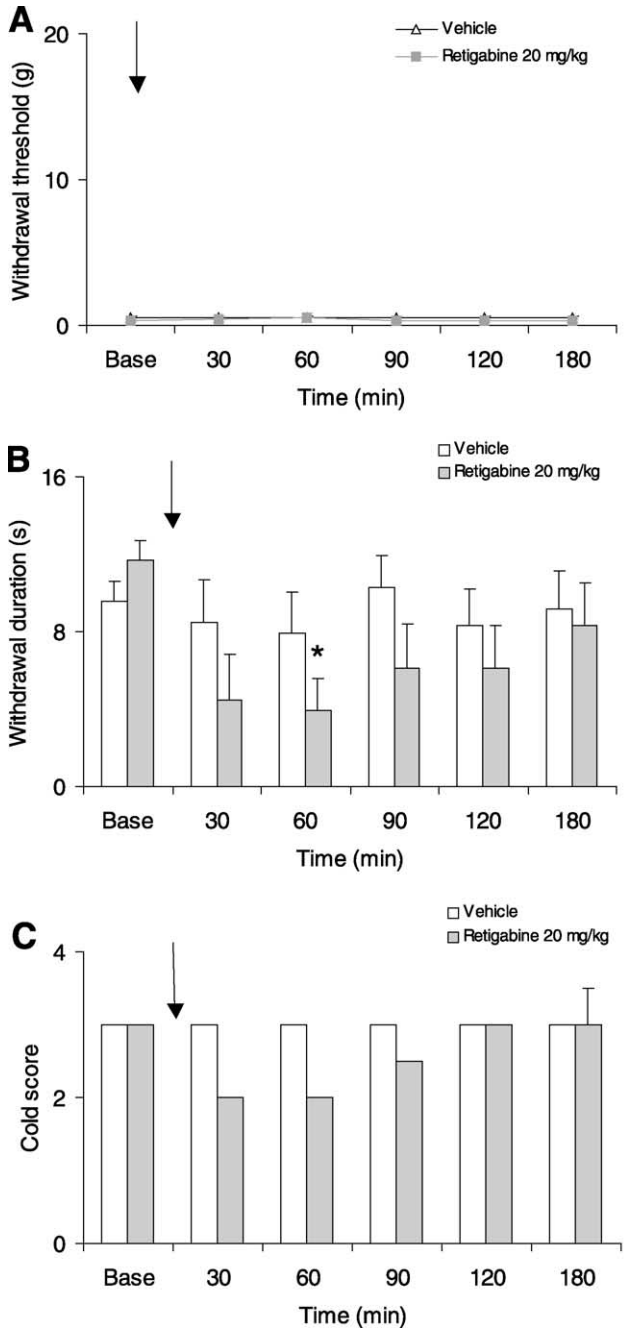

Fig. 2. Effects of retigabine on pain behaviours in spared nerve injury rats. Retigabine (20 mg/kg, p.o.) was administered 30 min before testing for (A) mechanical allodynia in response to von Frey stimulation, (B) mechanical hyperalgesia in response to pin prick stimulation and (C) cold allodynia in response to ethyl chloride cold spray stimulation of the injured hindpaw. Retigabine had no effect on mechanical or cold allodynia but did significantly attenuate mechanical hyperalgesia 60 min after administration. Data in (A) and (B) are presented as mean ± S.E.M. and in (C) as median ± MAD. *$P < 0.05$ vs. corresponding baseline. Both groups $n = 6$ animals.

number of flinches measured in rats pretreated with retigabine was significantly reduced by 40% ($P < 0.05$, one-way ANOVA) when compared with vehicle pretreated rats (151.3 ± 15.5 flinches, Fig. 3B). Pretreatment with XE-991 alone had no effect on the total number of flinches (148.4 ± 25.0) in response to formalin in the second phase

compared with vehicle pretreatment. However, for rats pretreated with XE-991 in combination with retigabine, the expected retigabine-induced inhibition of second-phase flinching behaviour was completely reversed (171.7 ± 9.3 flinches, $P < 0.05$ compared with retigabine alone).

3.3. Effects of retigabine and XE-991 in the tail flick test

In normal uninjured rats, administration of retigabine (20 mg/kg, p.o.) 30 min before testing had no effect on the tail flick latency compared with either baseline (5.6 ± 0.2 s) or the corresponding vehicle timepoint (5.8 ± 0.5 s) (Fig. 4). Similarly, administration of XE-991 (3 mg/kg, i.p.) had no effect on the tail flick latency compared with either baseline or vehicle-treated animals.

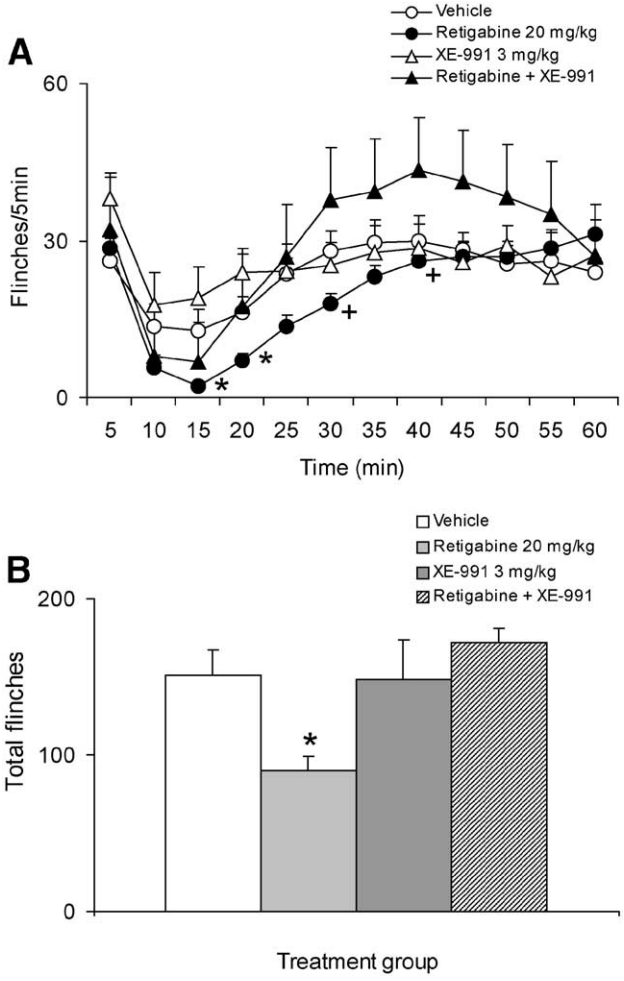

Fig. 3. Effects of XE-991 on retigabine-induced inhibition of flinching behaviour in the formalin test. (A) Retigabine (20 mg/kg, p.o.) and XE-991 (3 mg/kg, i.p.) were administered 30 and 5 min, respectively, before formalin injection, and the time course of drug actions followed. *$P < 0.05$ retigabine vs. XE-991, $^{+}P < 0.05$ retigabine vs. XE-991. (B) Retigabine significantly reduced the total number of flinches measured in the second phase of the formalin test. All data are presented as mean ± S.E.M. *$P < 0.05$ vs. all other treatment groups. All groups $n = 7–8$ animals.

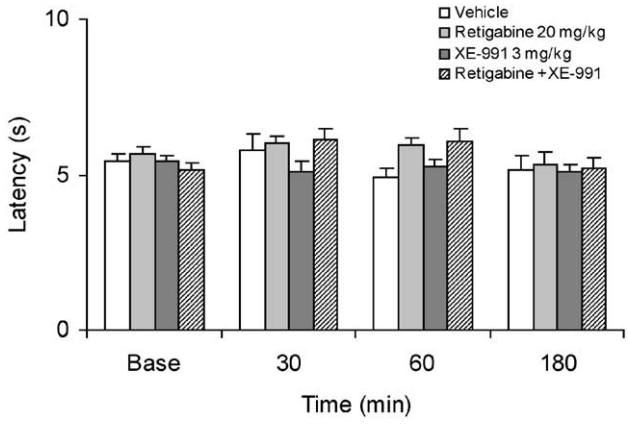

Fig. 4. Effects of retigabine and XE-991 on reflex pain responses in the tail flick test. Retigabine (20 mg/kg, p.o.) and XE-991 (3 mg/kg, i.p.) were administered 30 and 5 min, respectively, before application of a noxious thermal stimulus to the tip of the tail. Neither retigabine nor XE-991 had any effect on the tail flick latency compared with either the corresponding baseline or vehicle responses. All data are presented as mean ± S.E.M. All groups $n = 10$ animals.

3.4. Effects of retigabine in the rotarod test

Administration of retigabine (20 mg/kg, p.o.) in the rotarod test had no effect on motor performance in any of six animals monitored over the 2-min testing period. The highest dose of retigabine tested (40 mg/kg, p.o.) induced motor deficits in two out of six animals. Although this infers an ED_{50}>40 mg/kg required for retigabine to induce motor deficits by this mode of administration, it was decided that the lower dose of retigabine should be used for testing for potential anti-nociceptive effects.

4. Discussion

Retigabine is a structural analogue of flupirtine, which is a non-opiate, centrally acting analgesic used for relieving moderate pain of various types (Friedel and Fitton, 1993). The present study has shown for the first time that retigabine also has anti-nociceptive effects in rat models of persistent and chronic pain. Retigabine attenuated pain behaviours in two different models of nerve injury. In the formalin test, anti-nociceptive effects associated with retigabine administration were reversed by coadministration of the KCNQ blocker XE-991. The lack of effect of retigabine against an acute, noxious thermal stimulus indicates a selective interaction on nociceptive processing associated with pathophysiological events rather than with normal sensory nociceptive function.

Retigabine has a broad spectrum of anticonvulsant activity in animal seizure models, with in vitro studies suggesting a mechanism of action different to that described for other anticonvulsants (Kapetanovic and Rundfeldt, 1996). These drugs, which include lamotrigine and gabapentin, also have anti-nociceptive effects in animal models of neuropathic

pain (Hunter et al., 1997; Erichsen and Blackburn-Munro, 2002). Retigabine had mixed effects on sensitivity to mechanical stimulation of the injured hindlimb in the chronic constriction injury and spared nerve injury models of nerve injury. Mechanical hyperalgesia, in response to pin prick stimulation, was attenuated in both models, albeit to a greater extent in chronic constriction injury than spared nerve injury animals when comparable doses were tested. In contrast, the marked allodynia observed in response to tactile von Frey stimulation was unaffected by retigabine administration. We have seen similar effects for lamotrigine in spared nerve injury animals (Erichsen et al., 2003), whereas gabapentin has a marked anti-allodynic effect to mechanical stimulation in this model (Erichsen and Blackburn-Munro, 2002), a finding that has been essentially replicated using the Chung model of neuropathic pain (Hunter et al., 1997). The differential sensitivity of pain behaviours to anticonvulsant block in separate animal models of nerve injury (Hunter et al., 1997) was also evident within the current study. Whilst, sensitivity to cold stimulation was also attenuated by retigabine in chronic constriction injury animals, spared nerve injury animals were unaffected. Glutamate actions at *N*-methyl D-aspartate (NMDA) receptors within the spinal dorsal horn are a key component of central sensitising processes involved in the manifestation of other chronic pain states (Woolf and Salter, 2000). However, we have recently shown that spared nerve injury animals are also insensitive to anti-nociceptive actions of NMDA receptor antagonists (Erichsen and Blackburn-Munro, 2002) in contrast to other animal models of nerve injury (Yashpal et al., 2001). The analgesic actions of flupirtine have been attributed in part to activation of K^+ channels, which help to stabilise the membrane potential and contribute indirectly to NMDA receptor-mediated inhibition of neuronal activity. Whether a similar mechanism of action exists for retigabine remains to be established; although it is interesting to note that both flupirtine and retigabine prevent glutamate-induced toxicity in rat pheochromocytoma PC 12 cells (Seyfried et al., 2000). A consequence of such events might be the masking of any potential anti-nociceptive actions for retigabine in spared nerve injury animals, as a result of reduced glutamate receptor involvement in the aetiology of this model. Another explanation for these differences in pharmacological sensitivity of the individual models is that the injury produced to the nerve is qualitatively and mechanistically distinct (nerve constriction compared with nerve ligation) (Decosterd and Woolf, 2000; Erichsen and Blackburn-Munro, 2002), designed to simulate as closely as possible varying types of injury-induced nerve trauma observed in humans (Zimmerman, 2001).

Increased electrical excitability of dorsal root ganglion neurones, together with spontaneous activity arising from primary afferent fibres, arises as a consequence of axonal injury (Devor and Seltzer, 1999). Much of this injury-induced remodelling of sensory neurone function has been attributed to dynamic regulation of voltage-gated Na^+ channel expression within dorsal root ganglion neurones and at the site of injury (Waxman, 1999; Baker and Wood, 2001). Multiple voltage-gated K^+ channels have also been identified within dorsal root ganglion neurones. Recent studies suggest that they are also dynamically regulated after injury to peripheral nerves (Ishikawa et al., 1999; Rasband et al., 2001). Patch clamp recordings from cultured rat dorsal root ganglion neurones suggest that approximately three quarters of small cells (presumed nociceptors) sensitive to capsaicin have the M-current as the dominant subthreshold current (Selyanko et al., 2001). Taken together with the demonstration that KCNQ channel subunits are differentially expressed within specific subpopulations of dorsal root ganglion neurones (Karchewski et al., 2001) and the selective anti-nociceptive effects of retigabine after nerve injury, this suggests that KCNQ channel function and expression may also be regulated within dorsal root ganglion neurones after injury.

Increased electrical excitability of dorsal root ganglion neurones has also been shown after application of inflammatory mediators such as prostaglandin and adenosine (Gold et al., 1996b). It is generally agreed that the formalin test reproduces various aspects of acute inflammatory pain (Malmberg and Yaksh, 1995), where second-phase pain behaviours can be blocked by opiates and nonsteroidal anti-inflammatory drugs. Behavioural, electrophysiological and biochemical correlates of formalin-induced injury can also be attenuated by glutamate receptor antagonists (Dickenson and Sullivan, 1987; Chaplan et al., 1997; Yashpal et al., 2001). Thus, drug-induced anti-nociceptive effects in the formalin test can be used as a reliable indicator for potential anti-nociceptive effects in other pain models. Administration of retigabine selectively reduced flinching behaviour in the second phase of the formalin test in the current study, and this effect was completely reversed by the selective KCNQ channel blocker XE-991, indicating a mechanism of action mediated by KCNQ channels. When administered alone, XE-991 did not facilitate nociceptive processing in either phase of the formalin test compared with vehicle treatment. XE-991 was administered at the highest possible dose devoid of obvious side-effects as estimated from a preliminary behavioural observation study. The lack of pronociceptive effect observed for XE-991 suggests that KCNQ channels may not participate toward the increased excitability of sensory neurones after formalin injection. However, when activated by retigabine, they may then open and help to stabilise the membrane potential to restrain neuronal activity observed in the current study as an anti-nociceptive effect. Interestingly, the duration of retigabine actions against formalin-induced nociceptive behaviour was shorter than that observed for nociceptive behaviours in the nerve-injured animals. An obvious difference between the formalin test and the chronic constriction injury model are the far more pronounced changes in gene expression within sensory neurones and their spinal projection sites after nerve

injury (Wang et al., 2002). Any number of these nerve injury-induced plasticity changes might contribute to the enhanced anti-nociceptive actions of retigabine observed in the current study.

The tail flick test is primarily a spinally mediated reflex response to high threshold noxious thermal stimulation of the tail. In the current study, retigabine had no apparent anti-nociceptive effect on tail flick latency, indicating that KCNQ channels may have a minimal contribution to normal sensory nociceptive function. Nevertheless, the recent description of an M-like current involved in the regulation of spinal motoneurone excitability (Alaburda et al., 2002) suggests that drugs, which can directly modulate KCNQ channel function, may have a propensity for disturbing motor function. At the lowest dose tested (20 mg/kg, p.o.) in the rotarod test, retigabine was shown to be devoid of motor side-effects, a finding that agrees with previous observations (Tober et al., 1996).

In summary, we have shown for the first time that the anticonvulsant drug retigabine has anti-nociceptive effects in animal models of persistent and chronic pain, whilst normal nociceptive sensory processing is unaffected. These effects were mediated specifically via modulation of KCNQ channel function as shown by the full reversal of retigabine effects by the selective KCNQ blocker XE-991 in the formalin test. The future development of KCNQ channel openers, with increased potency compared with retigabine, might be expected to yield drugs with greater analgesic potential and improved side-effect profiles. Such drugs could provide an effective alternative to anticonvulsant drugs currently used in the treatment of neuropathic pain.

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