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A comparison of the antinociceptive effects of voltage-activated Na^+ channel blockers in two rat models of neuropathic pain

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Abstract

The pain-relieving effects of various voltage-activated Na^+ channel blockers have been evaluated in two rat models of neuropathic pain; the photochemically induced nerve injury model (Gazelius) and spared nerve injury model. Lidocaine (up to 40 mg/kg, i.p.) and lamotrigine (up to 60 mg/kg, i.p.) had no effect on mechanical or cold allodynia in either model. However, lamotrigine (10, 30 and 60 mg/kg) significantly attenuated mechanical hyperalgesia in the spared nerve injury model, while mexiletine (25 and 37.5 mg/kg, i.p.) attenuated mechanical allodynia in the Gazelius model. Tocainide (50, 75 and 100 mg/kg, i.p.) significantly reduced all types of pain behaviour measured. The present results show that these voltage-activated Na^+ channel blockers have broadly similar antinociceptive effects in these two models of neuropathic pain. They also show that these drugs can have markedly different effects on distinct neuropathic pain-related behaviours within models.

Keywords: Allodynia; Antiarrhythmic; Anticonvulsant; Gazelius nerve injury; Hyperalgesia; Spared nerve injury

1. Introduction

Pathophysiological changes occurring within damaged nerves as a result of injury can contribute to their injury-induced activation and induce a state of prolonged neuronal hyperexcitability within the dorsal horn of the spinal cord (Woolf and Salter, 2000). The associated behavioural hypersensitivity to noxious (hyperalgesia) and non-noxious (allodynia) stimuli can be difficult to treat with conventional analgesics (Arner and Meyerson, 1988), pre-empting the need to identify drugs with alternative mechanisms of action, which can provide adequate pain relief.

At least six of nine voltage-activated Na^+ channel pore-forming α-subunits ($Na_v1.1-1.9$) and three β-subunits (β1-3) have been detected in dorsal root ganglion neurones (Baker and Wood, 2001). These contribute to the two types of Na^+ current which have been identified in accordance with their pharmacological sensitivity to tetrodotoxin; tetrodotoxin-sensitive or tetrodotoxin-resistant Na^+ currents (Waxman, 1999; Baker and Wood, 2001). Altered Na^+ channel activity and gene expression in dorsal root ganglion neurones has been observed following nerve injury, and these changes may contribute to the increased sensitivity of primary afferent fibres associated with neuropathic pain (Waxman, 1999; Baker and Wood, 2001).

A number of local anaesthetics and anti-convulsant drugs have in common the ability to bind to voltage-activated Na^+ channels to prevent Na^+ influx into cells (Clare et al., 2000), and there is a substantial body of clinical evidence to suggest that such drugs can be effective in the treatment of neuropathic pain (McQuay et al., 1997; Backonja, 2001). Despite this, not all types of neuropathic pain patients respond to treatment with local anaesthetics (McQuay et al., 1997), and there is some dispute as to the true analgesic effectiveness of the anti-convulsant lamotrigine against neuropathic pain (McCleane, 1999, 2000). Animal behavioural models reflecting human neuropathic pain syndromes (Bennett and Xie, 1988; Kim

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and Chung, 1992; Gazelius et al., 1996) are used routinely for identifying novel drugs for treating neuropathic pain. The method used to induce the peripheral nerve injury varies, and as a consequence, the sensitivity of these models to drug treatments can differ as well (Zimmerman, 2001). In this study, we have compared the antinociceptive effects of the local anaesthetics lidocaine, mexiletine and tocainide, and lamotrigine, in two relatively new rat models of neuropathic pain; the photochemically induced nerve ischaemia model (Gazelius et al., 1996) and the spared nerve injury model (Decosterd and Woolf, 2000).

2. Materials and methods

2.1. Surgery

Adult male Sprague–Dawley rats (Möllegaard, Denmark) weighing 180–220 g on the day of surgery were used in this study. The experiments were performed according to the Ethical Guidelines of the International Association for the Study of Pain (Zimmerman, 1983) and were approved by local research ethic committees.

Ischaemic lesion of the sciatic nerve was produced as described previously (Kupers et al., 1998). Under chloral hydrate anaesthesia (300 mg/kg, i.p.), the right sciatic nerve was exposed at the midthigh level. Using a tunable argon ion laser (Innova model 70, Coherent Laser Products Division, CA, USA) operating at a wavelength of 514 nm with an average power of 0.17 W, the sciatic nerve was irradiated for 2 min. Immediately before the irradiation, erythrosin B (Aldrich, 32.5 mg/kg dissolved in 0.9% saline) was injected intravenously via a pre-inserted jugular vein catheter. After irradiation, the wound was closed in layers and the skin sutured together.

The spared nerve injury was produced as described previously (Decosterd and Woolf, 2000). The rats were anaesthetised with chloral hydrate (400 mg/kg, i.p.) and the sciatic nerve and its three terminal branches (sural, common peroneal and tibial nerves) 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 were removed. Any stretching or contact with the intact sural nerve was avoided. The wound was closed in layers and the skin sutured together with hidden stitches to avoid any opening of the wound by biting.

2.2. Behavioural testing

All behavioural tests were performed on animals at least 1 week after surgery. During testing, the rats were placed on an elevated metal grid allowing stimulation of the plantar surface (lateral aspect in spared nerve injury animals) of the hindpaw. The animals were allowed to habituate to the testing situation for at least 15 min before the experiment was initiated.

For mechanical stimulation, von Frey monofilaments (Stoelting, IL, USA) were 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 (Hao et al., 1999).

The response of the rats to cold stimulation was tested by spraying ethyl chloride (Perstrops, Sweden) onto the plantar surface of the hindpaw. The response was observed and classified according to the following scale: 0—no visible response; 1—startle response without paw withdrawal; 2—clear withdrawal of the paw; 3—prolonged withdrawal (duration 5–30 s) often combined with flinching and licking of the paw; 4—prolonged repetitive withdrawal (>30 s) and/or vocalization (Hao et al., 1999).

Only the spared nerve injury operated animals were tested for mechanical hyperalgesia using the pin prick test. The lateral plantar surface of the hindpaw was touched with the point of a safety pin at an intensity, which was insufficient to penetrate the skin. The duration of the paw withdrawal was recorded with a stopwatch. Prior to surgery, the withdrawal duration was too short to time accurately and was set to an arbitrarily minimal time of 0.5 s. A cut-off time of 15 s was applied to long withdrawals often seen for the nerve-injured paw (Decosterd et al., 1998).

2.3. Drugs

Lidocaine hydrochloride was obtained from Astra (Sweden) and mexiletine hydrochloride was purchased from Sigma. Tocainide hydrochloride (Tonocard® 50 mg/ml) was purchased from Hässle (Sweden) and lamotrigine was kindly supplied by GlaxoSmithKline (UK). Lidocaine and tocainide were obtained as pre-made solutions ready for injection. Mexiletine was dissolved in physiological saline and lamotrigine was suspended in 0.5% carboxymethylcellulose/0.5% tween 80. The animals with Gazelius nerve injury received all compounds while only lidocaine, tocainide and lamotrigine were tested in spared nerve injury rats, since we have previously reported on the antinociceptive effects of mexiletine in this model (Erichsen and Blackburn-Munro, 2002).

2.4. Statistics

Analysis of the data was performed using Sigmastat 2.03. Data for von Frey hair or pin prick stimulation are presented as mean ± S.E.M. To analyze the overall effects of the treatments, two-way repeated measure (RM) analysis of variance (ANOVA) was used, and for individual comparison Bonferroni's *t*-test was applied.

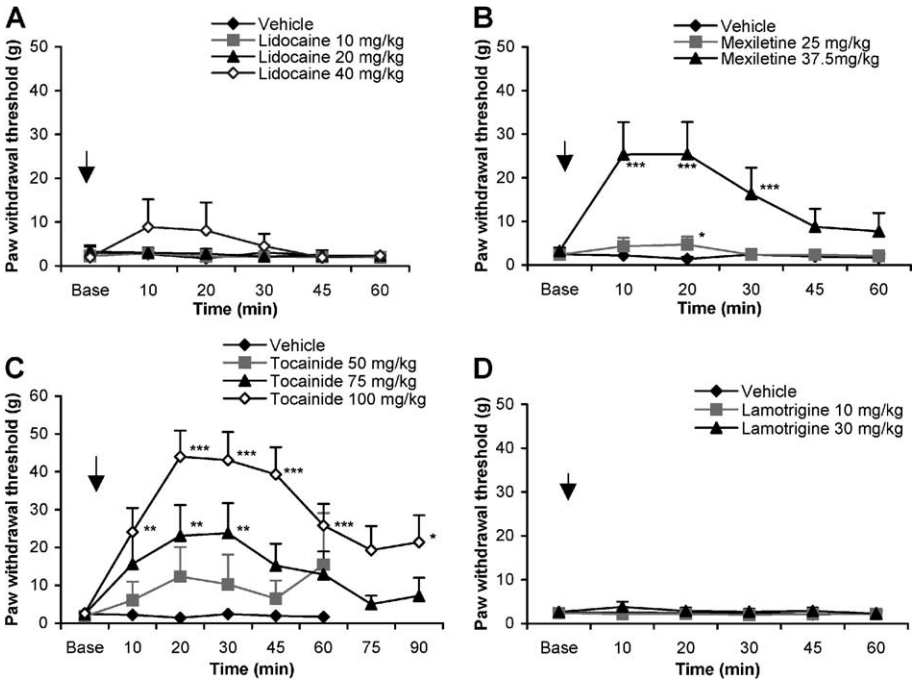

Fig. 1. Effects of i.p. (A) lidocaine (10, 20 and 40 mg/kg), (B) mexiletine (25 and 37.5 mg/kg), (C) tocainide (50, 75 and 100 mg/kg) and (D) lamotrigine (10 and 30 mg/kg) on mechanical allodynia in animals with Gazelius nerve injury. Drug injection is indicated by arrow. Data are presented as mean ± S.E.M. Six to eight animals were included in each group. $*P<0.05$, $**P<0.01$, $***P<0.001$ vs. baseline.

Data for cold stimulation are expressed as median ± me-median-derived absolute devision (MAD). Friedman RM ANOVA on Ranks was used to analyze the effects followed by Mann–Whitney Rank sum test for individual comparison. $P<0.05$ was considered to be statistically significant.

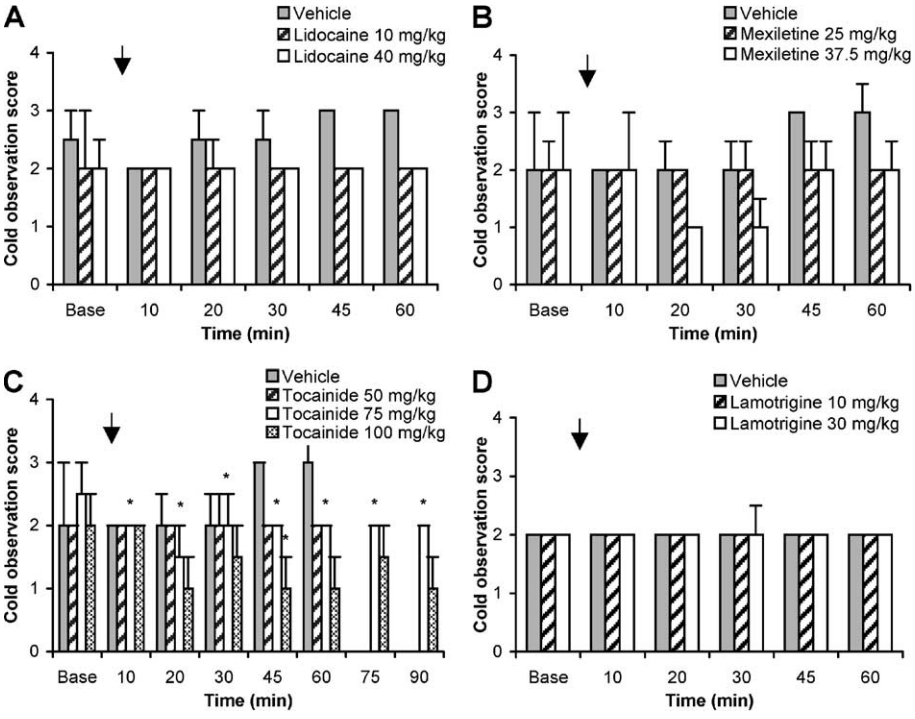

Fig. 2. Effects of i.p. (A) lidocaine (10, 20 and 40 mg/kg), (B) mexiletine (25 and 37.5 mg/kg), (C) tocainide (50, 75 and 100 mg/kg) and (D) lamotrigine (10 and 30 mg/kg) on cold allodynia in animals with Gazelius nerve injury. Drug injection is indicated by arrow. Data are presented as mean ± S.E.M. Six to eight animals were included in each group. $*P<0.05$ vs. baseline.

3. Results

3.1. General observations

In both the Gazelius and spared nerve injury models, pronounced mechanical allodynia (2.5 ± 0.5 and 0.3 ± 0.1 g) in response to von Frey hair stimulation of the injured hindpaw was observed, compared with pre-surgery levels which typically ranged from 5.7 to 51.1 g. Gazelius and spared nerve injury rats also showed marked cold allodynia (2.5 ± 0.5 and 3.0 ± 0.0 compared with a score of 0–1 before surgery) in response to ethyl chloride spray stimulation of the injured hindpaw. Only the spared nerve injury rats were tested with pin prick stimulation and showed marked mechanical hyperalgesia of the injured hindpaw (10.2 ± 0.2 s compared with <0.5 s before surgery).

3.2. Gazelius nerve injury model

Systemic administration of lidocaine (10, 20 and 40 mg/kg, i.p.) or lamotrigine (10 and 30 mg/kg, i.p.) had no effect on the paw withdrawal threshold for the injured hindlimb compared to the respective pre-injection baseline values (Fig. 1A and D). In contrast, mexiletine (37.5 mg/kg, i.p.) significantly increased ($P<0.001$, two-way RM ANOVA followed by Bonferroni's *t*-test) the withdrawal threshold in response to von Frey hair stimulation, 10 min after injection to 25.3 ± 7.4 g compared with baseline (3.3 ± 0.8 g), and this increase remained significant up to 30 min after injection (Fig. 1B). Injection of tocainide (75 and 100 mg/kg, i.p.) dose-dependently increased the paw withdrawal threshold in response to tactile stimulation (Fig. 1C). At the highest dose tested, tocainide significantly increased ($P<0.001$) the paw withdrawal threshold to 43.0 ± 6.9 g from a baseline value of 2.6 ± 0.5 g and this increase remained significant ($P<0.05$) at the final 90 min testing point.

Neither lidocaine, lamotrigine nor mexiletine had any effect on the cold observation score in response to hindpaw stimulation with ethyl chloride compared to the corresponding baseline level (Fig. 2A, B and D). However, injection of tocainide (75 mg/kg, i.p.) significantly attenuated ($P<0.05$, Friedman RM ANOVA on Ranks followed by Mann–Whitney Rank sum test) the cold score response to 2.0 ± 0, 10 min after injection compared with a baseline score of 2.5 ± 0.5 in the same animals (Fig. 2C). The attenuation in the cold response was dose-dependent (75 and 100 mg/kg, i.p.), 45 min after tocainide injection (2.0 ± 0 and 1.5 ± 0.5, respectively, both $P<0.05$), and remained for the 75 mg/kg dose throughout the entire testing period when compared with baseline.

3.3. Spared nerve injury model

Intraperitoneal administration of lidocaine (10 and 40 mg/kg) and lamotrigine (10, 30 and 60 mg/kg) had no effect on the paw withdrawal threshold in response to von Frey hair stimulation of the injured hindpaw compared to the respective pre-injection baseline values (Fig. 3A and C). Similarly, i.p. injection of tocainide (50 mg/kg) had no effect on the paw withdrawal threshold compared with baseline (Fig. 3B). However, at the highest dose tested in spared nerve injury animals, tocainide (75 mg/kg, i.p.) significantly increased ($P<0.001$) the withdrawal threshold in response to von

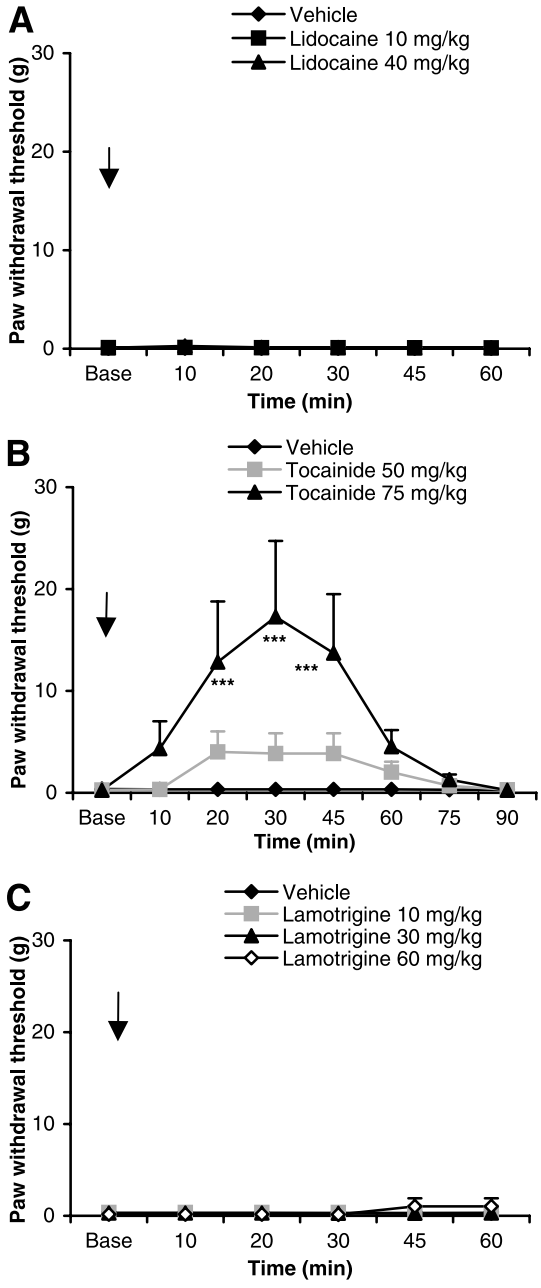

Fig. 3. Effects of i.p. (A) lidocaine (10 and 40 mg/kg), (B) tocainide (50 and 75 mg/kg) and (C) lamotrigine (10, 30 and 60 mg/kg) on mechanical allodynia in animals with spared nerve injury. Drug injection is indicated by arrow. Data are presented as mean±S.E.M. Six to eight animals were included in each group. ***$P<0.001$ vs. baseline.

Frey hair stimulation, 20 min after injection to 12.8 ± 5.9 g from a baseline value of 0.3 ± 0 g and this increase remained significant ($P < 0.001$) for a further 25 min of testing.

In spared nerve injury animals administered with either lidocaine or lamotrigine, there was no difference in the cold observation score compared with the corresponding baseline responses in the same animals (Fig. 4A and C). However, in animals administered with tocainide (50 and 75 mg/kg, i.p.), stimulation of the lateral surface of the injured hindpaw with ethyl chloride was associated with a significant decrease (both $P < 0.05$) in the cold observation score to 2 ± 0, 20 min after injection from a baseline score of 3 ± 0. This effect lasted for up to 75 min for the highest dose of tocainide tested (Fig. 4B).

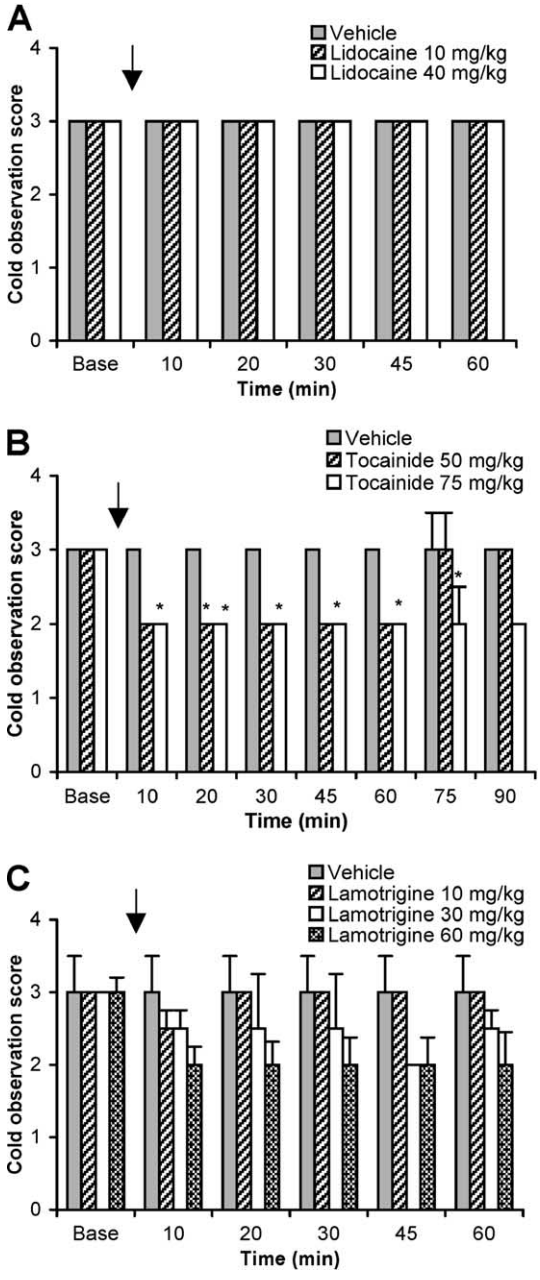

Fig. 4. Effects of i.p. (A) lidocaine (10 and 40 mg/kg), (B) tocainide (50 and 75 mg/kg) and (C) lamotrigine (10, 30 and 60 mg/kg) on cold allodynia in animals with spared nerve injury. Drug injection is indicated by arrow. Data are presented as mean±S.E.M. Six to eight animals were included in each group. *P<0.05 vs. baseline.

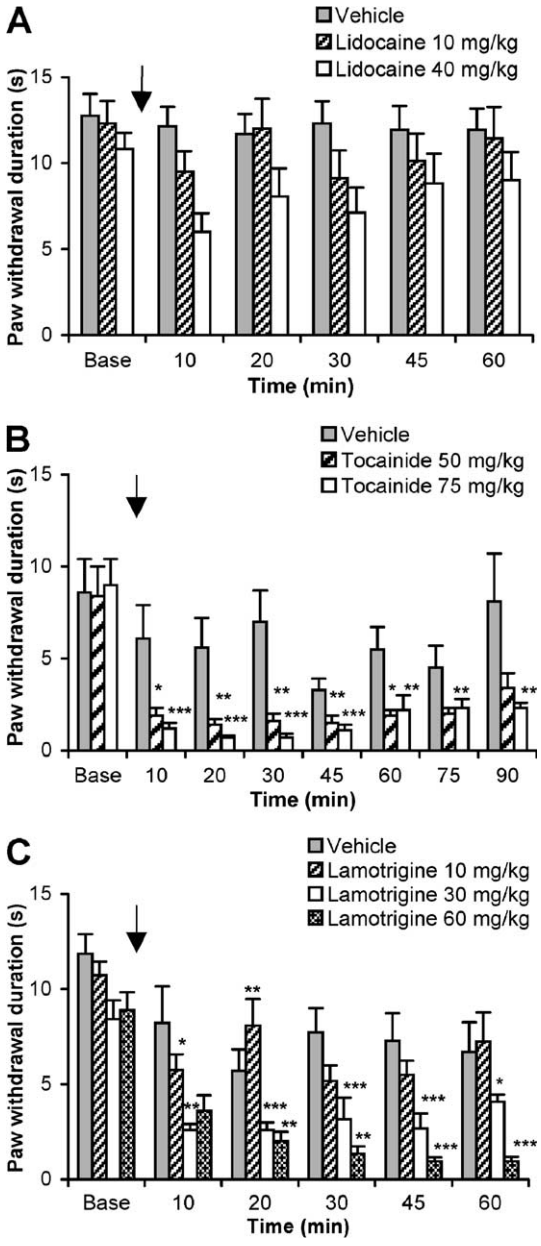

Fig. 5. Effects of i.p. (A) lidocaine (10 and 40 mg/kg), (B) tocainide (50 and 75 mg/kg) and (C) lamotrigine (10, 30 and 60 mg/kg) on mechanical hyperalgesia in animals with spared nerve injury. Drug injection is indicated by arrow. Data are presented as mean±S.E.M. Six to eight animals were included in each group. *P<0.05, **P<0.01, ***P<0.001 vs. baseline.

Intraperitoneal administration of lidocaine to spared nerve injury animals had no significant effect on the paw withdrawal duration in response to pin prick stimulation of the injured hindpaw (Fig. 5A). In contrast, 10 min after

injection of tocainide (50 and 75 mg/kg, i.p.), there was a dose-dependent attenuation ($P<0.05$ and $P<0.001$, respectively, two-way RM ANOVA followed by Bonferroni's *t*-test) in the paw withdrawal response to 1.9 ± 0.4 and 1.2 ± 0.3 s from corresponding baseline values of 7.8 ± 1.7 and 8.3 ± 1.6 s. At the highest dose of tocainide tested (75 mg/kg, i.p.), the reduction in the paw withdrawal response remained significantly different ($P<0.01$) compared with the pre-injection baseline response throughout the entire testing period (Fig. 5B). Injection of lamotrigine (10 and 30 mg/kg, i.p.) was similarly associated with a dose-dependent reduction ($P<0.05$ and $P<0.01$, respectively) in the paw withdrawal response to 1.9 ± 0.4 and 1.2 ± 0.3 s from corresponding baseline values of 7.8 ± 1.7 and 8.3 ± 1.6 s 10 min after injection (Fig. 5C). For the two highest doses of lamotrigine tested (30 and 60 mg/kg, i.p.), this effect remained significant ($P<0.05$ and $P<0.001$, respectively) for up to 60 min after injection.

4. Discussion

The present study has compared the pain-relieving effects of various voltage-activated Na^+ channel blockers in two separate rat models (spared nerve injury and Gazelius) of neuropathic pain. We have previously reported that systemic administration of mexiletine to spared nerve injury rats can markedly attenuate pain behaviours (Erichsen and Blackburn-Munro, 2002), and here we have extended this observation to show that mexiletine can also attenuate pain behaviours in Gazelius animals. In addition, we have shown that systemic administration of tocainide, in contrast to lidocaine and to a lesser extent lamotrigine, has marked antinociceptive effects in both nerve injury models.

Injury to peripheral nerves is associated with increases in the electrical excitability of dorsal root ganglion neurones together with spontaneous activity arising from damaged primary afferent fibres (Devor and Seltzer, 1999). Much of the injury-induced remodelling of sensory neurone function has been attributed to dynamic regulation of voltage-activated Na^+ channel expression within dorsal root ganglion neurones and at the site of injury (Waxman, 1999; Baker and Wood, 2001). Electrophysiological studies have shown that lidocaine, mexiletine and tocainide can decrease both the spontaneous activity and the mechanical sensitivity of rat neuromas (Chabal et al., 1989), while lidocaine has additionally been shown to block ectopic activity from dorsal root ganglion cells (Devor et al., 1992).

Using the conditions employed for testing in this study, we were unable to show any antinociceptive effects for intraperitoneally administered lidocaine in either model tested. This was somewhat surprising given that intravenous administration of lidocaine has previously been reported to attenuate mechanical sensitivity to noxious stimulation in other models of neuropathic pain (Abram and Yaksh, 1994; Abdi et al., 1998). It is possible that these differences may have been due to insufficient plasma levels of lidocaine being attained, since both the route and rate of administration of lidocaine seem to be an important determinant of the outcome in alleviating neuropathic pain behaviours (Chaplan et al., 1995).

Similarly, mexiletine has been reported to alleviate both mechanical allodynia and hyperalgesia in the Chung nerve ligation model (Jett et al., 1997). Our present results show that mexiletine also attenuates tactile allodynia in Gazelius animals, at the same dose (37.5 mg/kg, i.p.), and with a similar onset and duration of action to that previously observed for spared nerve injury animals (Erichsen and Blackburn-Munro, 2002). Although mechanical hyperalgesia of the injured hindlimb was not tested in Gazelius animals, the similarity of the anti-allodynic effect for mexiletine in both models, suggests that mexiletine may also have an effect against mechanical hyperalgesia in Gazelius animals.

In both the Gazelius and spared nerve injured animals, tocainide inhibited all pain behaviours tested. Although a higher dose of tocainide (100 mg/kg) was tolerated in Gazelius nerve injured rats, when administered at 75 mg/kg, tocainide showed marked antinociceptive effects in both neuropathic pain models. This agrees with other behavioural observations where tocainide relieves pain behaviours in spinally injured rats (Hao et al., 1992). However, tocainide in contrast to lidocaine and mexiletine is not used in the clinical treatment of neuropathic pain due to haematological adverse effects (Xu et al., 1992).

Although lamotrigine has previously been reported to attenuate cold allodynia in other models of nerve injury (Hunter et al., 1997), we were not able to replicate these findings in either the Gazelius or spared nerve injury models. In contrast, lamotrigine did appear to reduce mechanical hyperalgesia in response to pin prick stimulation in a dose-dependent manner in the spared nerve injury model, which is in general agreement with previously reported effects of lamotrigine on both prostaglandin E_2- and streptozotocin-induced mechanical hyperalgesia (Nakamura-Craig and Follenfant, 1995). One of the defining features of neuropathic pain is a pronounced hypersensitivity to innocuous mechanical stimulation of the skin. Despite the increasing use of lamotrigine in the clinical treatment of neuropathic pain, some controversy exists as to its true efficacy in this condition (McCleane, 1999, 2000). There appears to be a need to administer in incremental doses over an extended period of time in human patients to achieve maximum analgesic benefit. A similar explanation may account for the surprising lack of effect of lamotrigine against mechanical allodynia observed for both nerve injury models in the current study.

Mexiletine and tocainide are oral congeners of lidocaine, with local anaesthetic and antiarrhythmic actions similar to lidocaine (Xu et al., 1992). Lamotrigine is structurally

unrelated to the antiarrhythmics. However, all four drugs tested have in common the ability to preferentially bind and stabilize inactivated states of the Na^+ channel to prevent Na^+ influx into cells (Ragsdale and Avoli, 1998; Clare et al., 2000). Referred to as state-dependent or use-dependent block, this shared binding mechanism endows these compounds with the ability to selectively inhibit Na^+ channels during sustained depolarisation such as that incurred in the setting of tissue injury, and allows control of membrane excitability without compromising normal function of the channel (Ragsdale and Avoli, 1998; Clare et al., 2000). As the membrane potential becomes more depolarised as occurs in the setting of tissue injury, lamotrigine and mexiletine appear to be more effective use-dependent blockers of tetrodotoxin-resistant than tetrodotoxin-sensitive currents, than other voltage-activated Na^+ channel blockers such as carbamazepine (Brau et al., 2001). In this regard, the downregulation of tetrodotoxin-resistant currents within dorsal root ganglion neurones that occurs after nerve injury (Baker and Wood, 2001) may account for the relative lack of antinociceptive effects observed for lamotrigine in these models. However, this cannot be the sole explanation, based on the more encouraging results achieved with mexiletine against neuropathic pain behaviours in these models (Erichsen and Blackburn-Munro, 2002).

Recently, this class of drugs have been shown to bind to specific amino acid residues in an overlapping but non-identical binding site located on the inner surface of the Na^+ channel pore (Ragsdale and Avoli, 1998), with differing pharmacokinetic properties (Kuo et al., 1997). It is likely that the shared binding mechanism is also responsible for these drugs being able to relieve neuropathic pain in humans (Lindstrom and Lindblom, 1987; Mao and Chen, 2000; Backonja, 2001). Whether subtle differences in the way and rate that these drugs bind within the pore is reflected by the inability of lidocaine to affect any of the measured pain behaviours in either model, or provides an alternative explanation for lamotrigine to affect sensitivity to tactile stimulation in either model, remains to be established. In view of the marked antinociceptive effects observed for tocainide in the current study however, and in the face of its neurotoxic effects in humans, this point appears to merit further investigation.

In summary, we have shown that drugs capable of blocking voltage-activated Na^+ channels are effective at relieving pain behaviours in two separate models of peripheral nerve injury. Overall, the antinociceptive effects observed for lidocaine, mexiletine, tocainide and lamotrigine were broadly similar between the two models, although they were markedly selective towards specific pain behaviours within either model. Whether these points arise as a result of the maximum dose of drug, which could be tolerated without overt side effect issues, or reflects discriminatory binding properties towards voltage-activated Na^+ channels, requires further testing. These results further support the argument for selective targeting of Na^+ channel functioning in the treatment of neuropathic pain.

Acknowledgements

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References

Abdi, S., Lee, D.H., Chung, J.M., 1998. The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. Anesth. Analg. 87, 1360–1366.

Abram, S.E., Yaksh, T.L., 1994. Systemic lidocaine blocks nerve injury-induced hyperalgesia and nociceptor-driven spinal sensitization in the rat. Anesthesiology 2, 383–391.

Arner, S., Meyerson, B.A., 1988. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain 33, 11–24.

Backonja, M., 2001. Anticonvulsants and antiarrthymics in the treatment of neuropathic pain syndromes. In: Hansson, P.T., Fields, H.L., Hill, R.G. (Eds.), Neuropathic Pain: Pathophysiology and Treatment, Progress in Pain Research and Management. IASP Press, Seattle, pp. 185–201.

Baker, M.D., Wood, J.N., 2001. Involvement of Na^+ channels in pain pathways. Trends Pharmacol. Sci. 22, 27–31.

Bennett, G.J., Xie, Y.K., 1988. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33, 87–107.

Brau, M.E., Dreimann, M., Olschewski, A., Vogel, W., Hempelmann, G., 2001. Effect of drugs used for neuropathic pain management on tetrodotoxin-resistant Na^+ currents in rat sensory neurones. Anesthesiology 94, 137–144.

Chabal, C., Russell, L.C., Burchiel, K.J., 1989. The effect of intravenous lidocaine, tocainide, and mexiletine on spontaneously active fibers originating in rat sciatic neuromas. Pain 38, 333–338.

Chaplan, S.R., Bach, F.W., Shafer, S.L., Yaksh, T.L., 1995. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. Anesthesiology 83, 775–785.

Clare, J.J., Tate, S.N., Nobbs, M., Romanos, M.A., 2000. Voltage-gated sodium channels as therapeutic targets. Drug Discov. Today 5, 506–520.

Decosterd, I., Woolf, C.J., 2000. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain 87, 149–158.

Decosterd, I., Buchser, E., Gilliard, N., Saydoff, J., Zurn, A.D., Aebischer, P., 1998. Intrathecal implants of bovine chromaffin cells alleviate mechanical allodynia in a rat model of neuropathic pain. Pain 76, 159–166.

Devor, M., Seltzer, Z., 1999. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall, P.D., Melzack, R. (Eds.), Textbook of Pain. Churchill Livingstone, London, pp. 129–164.

Devor, M., Wall, P.D., Catalan, N., 1992. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain 48, 261–268.

Erichsen, H.K., Blackburn-Munro, G., 2002. Pharmacological characterisation of the spared nerve injury model of neuropathic pain. Pain 98, 151–161.

Gazelius, B., Cui, J.G., Svensson, M., Meyerson, B., Linderoth, B., 1996. Photochemically induced ischaemic lesion of the rat sciatic nerve. A novel method providing high incidence of mononeuropathy. NeuroReport 7, 2619–2623.

Hao, J.X., Yu, Y.X., Seiger, Å., Wiesenfeld-Hallin, Z., 1992. Systemic tocainide relieves mechanical hypersensitivity and normalizes the responses of hyperexcitable dorsal horn wide-dynamic-range neurons after transient spinal cord ischemia in rats. Exp. Brain Res. 91, 229–235.

Hao, J.X., Xu, I.S., Xu, X.J., Wiesenfeld-Hallin, Z., 1999. Effects of intrathecal morphine, clonidine and baclofen on allodynia after partial sciatic nerve injury in the rat. Acta Anaesthesiol. Scand. 43, 1027–1034.

Hunter, J.C., Gogas, K.R., Hedley, L.R., Jacobson, L.O., Kassotakis, L., Thompson, J., Fontana, D.J., 1997. The effect of novel anti-epileptic drugs in rat experimental models of acute and chronic pain. Eur. J. Pharmacol. 324, 153–160.

Jett, M.F., McGuirk, J., Waligora, D., Hunter, J.C., 1997. The effects of mexiletine, desipramine and fluoxetine in rat models involving central sensitization. Pain 69, 161–169.

Kim, S.H., Chung, J.M., 1992. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 50, 355–363.

Kuo, C.C., Chen, R.S., Lu, L., Chen, R.C., 1997. Carbamazepine inhibition of neuronal Na^+ currents: quantitative distinction from phenytoin and possible therapeutic implications. Mol. Pharmacol. 51, 1077–1083.

Kupers, R., Yu, W., Persson, J.K., Xu, X.J., Wiesenfeld-Hallin, Z., 1998. Photochemically-induced ischemia of the rat sciatic nerve produces a dose-dependent and highly reproducible mechanical, heat and cold allodynia, and signs of spontaneous pain. Pain 76, 45–59.

Lindstrom, P., Lindblom, U., 1987. The analgesic effect of tocainide in trigeminal neuralgia. Pain 28, 45–50.

Mao, J., Chen, L.L., 2000. Systemic lidocaine for neuropathic pain relief. Pain 87, 7–17.

McCleane, G., 1999. 200 mg of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind placebo controlled trial. Pain 83, 105–107.

McCleane, G., 2000. Reply to Jaques Devulder. Pain 86, 211–212.

McQuay, H.J., Moore, R.A., Eccleston, C., Morley, S., de Williams, A.C., 1997. Systematic review of outpatient services for chronic pain control. Health Technol. Assess. 1, 1–137.

Nakamura-Craig, M., Follenfant, R.L., 1995. Effect of lamotrigine in the acute and chronic hyperalgesia induced by PGE_2 and in the chronic hyperalgesia in rats with streptozotocin-induced diabetes. Pain 63, 33–37.

Ragsdale, D.S., Avoli, M., 1998. Sodium channels as molecular targets for antiepileptic drugs. Brains Res. Rev. 26, 16–28.

Waxman, S.G., 1999. The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. Pain S6, S133–S140.

Woolf, C.J., Salter, M.W., 2000. Neuronal plasticity: increasing the gain in pain. Science 288, 1765–1769.

Xu, X.J., Hao, J.X., Seiger, Å., Arner, S., Lindblom, U., Wiesenfeld-Hallin, Z., 1992. Systemic mexiletine relieves chronic allodynia like symptoms in rats with ischemic spinal cord injury. Anesth. Analg. 74, 649–652.

Zimmerman, M., 1983. Ethical guidelines for investigations of experimental pain in conscious animals. Pain 16, 109–110.

Zimmerman, M., 2001. Pathobiology of neuropathic pain. Eur. J. Pharmacol. 429, 23–37.