


Persistent secondary hyperalgesia after gastrocnemius incision in the rat

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Secondary hyperalgesia, an exaggerated response to stimuli applied to undamaged tissue surrounding an injury, is a common consequence of tissue injury and inflammation. It is well established that the etiology of secondary hyperalgesia is sensitization of central neurons but the exact mechanism and its role in certain clinical pain states is unclear. In the present experiments, we studied responses to punctate and non-punctate mechanical stimuli and to heat applied to the plantar aspect of the hindpaw remote to an incision in the gastrocnemius region of the rat hindlimb. Median withdrawal thresholds to von Frey filaments were reduced 2 h after incision of skin, fascia and muscle (gastrocnemius incision, n = 9) and remained reduced through postoperative day 6 (p < 0.05 vs sham). Only a transient reduction in withdrawal threshold occurred after incision of skin and fascia (skin incision, n = 10). No enhanced responsiveness to blunt mechanical stimulation or reduction in withdrawal latency to heat was present after gastrocnemius incision (p > 0.05 vs sham, n = 9 each group). Reduced withdrawal thresholds were blocked by i.t. administration of morphine and by local anesthetic injection at the test site 2 h and 2 days after gastrocnemius incision. These pharmacological data provide evidence that reduced withdrawal thresholds after gastrocnemius incision are nociceptive behaviors indicating persistent secondary hyperalgesia. Because the behaviors have a similar time course to secondary hyperalgesia in postoperative patients, the model will be useful to evaluate the mechanisms for secondary mechanical hyperalgesia after incision, its pharmacological characteristics and its potential role in persistent postoperative pain. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS: central sensitization, postoperative pain, punctate mechanical stimuli, acute pain.

INTRODUCTION

Enhanced sensitivity to mechanical stimuli is a common consequence of tissue injuries and inflammation. Mechanical sensitivity can occur at the site of tissue damage (primary mechanical hyperalgesia) where it is usually accompanied by hyperalgesia to heat and also in uninjured tissue surrounding the injury (secondary mechanical hyperalgesia,Coderre and Katz, 1997; Raja et al., 1999). Based on psychophysical and neurophysiological experiments, it is well established that primary hyperalgesia to heat and at least in part to mechanical stimuli is mediated by sensitization of primary afferent fibers (Meyer, 1995). Because sensitization of afferent fibers cannot explain secondary mechanical hyperalgesia, secondary hyperalgesia is considered a consequence of central sensitization (Coderre and Katz, 1997; Millan, 1999; Raja et al., 1999).

To gain greater insight into the phenomenon of secondary hyperalgesia, a variety of animal (Sluka and Westlund, 1993; Gilchrist et al., 1996; Nozaki-Taguchi and Yaksh, 1998) and human (Raja et al., 1984; LaMotte et al., 1991; Cervero et al., 1993; Petersen and Rowbotham, 1999) pain models have been developed. In general, the
results suggest that secondary punctate mechanical hyperalgesia represents an enhanced response to input from non-sensitized afferent fibers but the exact mechanisms remain unclear (McMahon et al., 1993; Millan, 1999; Raja et al., 1999; Treede and Magerl, 2000). In clinical acute pain, an area of secondary mechanical hyperalgesia is present in uninjured areas surrounding incisions in postoperative patients (Richmond et al., 1993; Stubbau et al., 1997). This indicates that central sensitization occurs after surgery; however, the role of secondary hyperalgesia and central sensitization in postoperative pain is not known.

We have previously developed a rat model for postoperative pain (Brennan et al., 1996). In this model, reduced withdrawal thresholds to von Frey filaments applied adjacent to the incision occur suggesting primary hyperalgesia to punctate mechanical stimuli. Secondary punctate hyperalgesia after plantar incision is also present but short lived (Zahn and Brennan, 1999b). In the present study we demonstrate persistent secondary hyperalgesia after incision in the gastrocnemius region of the rat hindlimb so that future studies can examine mechanisms of central sensitization and secondary hyperalgesia and its importance for pain after surgery. Portions of these data have been reported in abstract form (Pogatzki et al., 2001).

MATERIALS AND METHODS

General

After approval from the Institution’s Animal Care and Use Committee, the experiments were performed on 100 adult male Sprague-Dawley rats (250–300g, Harlan, Indianapolis, IN) in accordance with the Ethical Guidelines for Investigations of Experimental Pain in Conscious Animals. Rats were housed in pairs before and individually after surgery on clean bedding of organic cellulose fiber (Shepherd Specialty Papers, Inc., Kalamazoo, MI); food and water were unrestricted. All rats were euthanized at the end of the protocol with an overdose of a mixture of pentobarbital and phenytoin injected intraperitoneally.

Incisions

Incisions were made at the right posterior hindlimb using halothane for anesthesia. Prior to surgery, each rat received an injection of penicillin, 30000IU in the triceps. Control rats underwent a sham procedure that included anesthesia and preparation of the posterior hindlimb but no incision.

Skin incision

The skin of the posterior right hindlimb was shaved distal to the knee and prepared with povidone–iodine. A 3 cm longitudinal incision was made with a number 11 blade through the skin of the midportion of the posterior hindlimb starting 1–1.5 cm from the edge of the heel and extending to the popliteal region. Using blunt dissection, the cutaneous tissue was separated from the underlying muscle. After hemostasis with gentle pressure, the skin was opposed with three mattress sutures of 5-0 nylon on an FS-2 needle and the incision was covered with a mixture of polymixin B, neomycin and bacitracin ointment. Sutures were removed 3 days after the incision was made.

Gastrocnemius incision

After shaving and sterile preparation of the posterior hindlimb, the skin was incised as described above. The cutaneous tissue was separated from the underlying muscle, the gastrocnemius muscle was split and divided by blunt dissection. The divided muscle was retracted. The tendons, the origin and the insertion remained intact. The skin was closed and treated as described above; sutures were removed on postoperative day 3.

Intrathecal (i.t.) catheter placement

A lumbar i.t. catheter was placed in 30 rats for drug administration using a technique described previously (Pogatzki et al., 2000). Briefly, under 2% halothane anesthesia, the skin over the lumbar vertebrae was cleansed and incised. The
Secondary Hyperalgesia After Gastrocnemius Incision

The intervertebral space between L5 and L6 was punctured with a hypodermic needle and a 32G polyurethane catheter (32-PU, outer diameter 0.010 in and inner diameter 0.005 in; Micor, Allison Park, PA) was inserted i.t. The distal end was connected to PE-10, tunneled to the cervical region, flushed with saline and sealed. The i.t. position was tested 3–6 h after recovery from anesthesia by an injection of 20 μl of 2% lidocaine and observation of rapid hindlimb paralysis. The position was confirmed at the end of the experiment by injecting 30 μl of methylene blue, euthanizing the rat, dissecting the lumbar spinal cord and observing the blue-stained lumbar spinal cord.

Experimental protocols

On the day of the experiment, rats were placed individually on an elevated plastic mesh floor covered with a clear plastic cage top (21 cm × 27 cm × 15 cm) and allowed to acclimate. All stimuli were applied to the plantar aspect of the hindpaw approximately 20 mm from the incision (Fig. 1). Responses to the punctate mechanical stimuli and to the non-punctate mechanical stimulus and radiant heat were studied in separate groups (protocols A and B, Table 1). Similarly, the effects of bupivacaine infiltration (protocol C) and i.t. morphine (protocol D) were assessed in separate groups. The experimenter was blinded to the type of incision performed and to the drug injected.

Protocol A: Responses to punctate mechanical stimuli

In 28 rats, baseline withdrawal thresholds to punctate mechanical stimuli were determined as described previously (Zahn and Brennan, 1999b). Briefly, calibrated Semmes Weinstein von Frey filaments (13, 24, 41, 61, 89, 108, 131, 280 and

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Protocol A: effect of gastrocnemius incision on response to punctate mechanical stimuli. Protocol B: effect of gastrocnemius incision on response to a non-punctate mechanical stimulus and to radiant heat. Protocol C: effect of a local anesthetic (LA) injection at the test site on response to punctate mechanical stimuli 2 h (groups 1, 2) and 2 days after gastrocnemius incision (groups 3, 4). Protocol D: effect of i.t. morphine on response to punctate mechanical stimuli 2 h (groups 1, 2) and 2 days (groups 3, 4) after gastrocnemius incision. n, number of rats. Test time for protocols A, B, C and D corresponds to Figs 1, 2, 3 and 4 respectively.

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522 mN bending force, Stoelting, Indianapolis, IN) were applied once for approximately 1 s starting with 13 mN and continuing until a withdrawal response occurred or 280 mN was reached. If there was no withdrawal response, 522 mN was recorded. This was repeated twice and the lowest force from three tests producing a response was considered the withdrawal threshold. After baseline tests, rats underwent sham procedure, skin incision or gastrocnemius incision as described above; withdrawal thresholds to punctate mechanical stimuli were assessed at times shown in Table 1.

**Protocol B: Responses to blunt mechanical stimulation and to radiant heat**

For assessing responses to blunt mechanical stimulation, a circular plastic disk (5 mm diameter) attached to a von Frey filament (400 mN) was applied from underneath the mesh to the plantar aspect of the paw (Fig. 2A); withdrawal or lifting the foot off the mesh without bending the filament was considered a response. The response frequency was calculated from three tests separated by 10 min. In the same rat, withdrawal latency to heat was measured by applying a focused radiant heat source from underneath a glass floor (3 mm thick) to the plantar aspect of the paw (Fig. 2B). The heat stimulus was light from a 50 W projector lamp with an aperture diameter of 6 mm that illuminates a circular area with a diameter of 8 mm. Before the study began, the intensity was adjusted so that the withdrawal latency was approximately 10–12 s. The average withdrawal latency was calculated from three trials 10–15 min apart (Zahn and Brennan, 1999b). Eighteen rats were pre-tested for responses to non-punctate mechanical stimulus and to heat; sham procedure or gastrocnemius incision was performed and responses to the plastic disc and heat were measured (Table 1).

**Protocol C: Effect of bupivacaine infiltration at the test site**

It is possible that application of von Frey filaments to the paw after gastrocnemius incision causes distortion of the incised tissue at the lower leg. This could lead to activation of primary afferent fibers in the incision area even though the stimulus is distant to the test site. To confirm that the test stimuli were only affecting afferents at the plantar area, bupivacaine was infiltrated to block afferent fiber responses to von Frey filaments at the test site. If a withdrawal response to filament application still occurred then it was likely that stimulus distorts the incision causing withdrawal.

In 12 rats, withdrawal thresholds to the filaments were measured before (Pre) and 2 h (time 0) after the gastrocnemius incision was made. Then, under brief halothane anesthesia, a 30 gauge needle was advanced subcutaneously from the lateral border of hairy and glabrous skin to the test site and 100 μl of 0.9% saline (vehicle) or 100 μl of 0.5% bupivacaine was infiltrated into the proximal part of the hindpaw; withdrawal thresholds were assessed after infiltration as shown in Table 1. In 12 other rats, the effect of local anesthetic infiltration was also determined 2 days after gastrocnemius incision as shown in Table 1 (groups 3, 4). In these rats, no injection was made on the day of incision.

**Protocol D: Effect of i.t. morphine on responses to punctate mechanical stimulation**

Eighteen rats with i.t. catheters were tested for withdrawal threshold to von Frey filaments before gastrocnemius incision (Pre) and 2 h after incision (time 0); either vehicle (saline 0.9%, 5 μl, group 1) or morphine (5 μg/5 μl, group 2) was administered i.t. and pain behavior assessed as shown in Table 1. The dose was chosen based on studies of primary hyperalgesia (Zahn et al., 1997). In 12 other rats, the effect of i.t. morphine on secondary punctate mechanical hyperalgesia was tested on postoperative day 2 (Table 1, groups 3, 4). These rats did not receive i.t. morphine on the day of incision. To limit the number of animals used and to avoid repeated doses of morphine in the same rat, some of these rats received a single injection of a non-N-methyl-D-aspartate receptor antagonist 2 h after gastrocnemius incision. No residual analgesic drug effect from the previous treatment was evident.
2 days later, they were used to test morphine on postoperative day 2.

Drugs

Bupivacaine (5 mg/ml), lidocaine (20 mg/ml) and preservative-free morphine sulfate (1 mg/ml) were purchased from Abbott Laboratories. The dose of morphine administered i.t. was based on the amount of morphine sulfate and injected in a volume of 5 μl followed by a 10 μl flush of preservative-free saline. Preservative-free saline was used as a vehicle.

Statistics

Because heat withdrawal latencies are continuous data, the data were compared using parametric analyses. A two-way analysis of variance (ANOVA) for repeated measures and subsequent one-way ANOVA were performed. Multiple comparisons within groups following the one-way ANOVA were performed using a two-tailed Dunnett test. Data for mechanical stimuli are not continuous and were compared using non-parametric tests. Friedman’s test for within-group and the Kruskal–Wallis test (three groups) and Wilcoxon–Mann–Whitney test (two groups) for between-group comparisons were used. Multiple comparisons following Friedman’s test and the Kruskal–Wallis test were performed using a two-tailed Dunnett and Dunn test respectively. The results are expressed as median or mean ± standard deviation (SD) when appropriate. p < 0.05 was considered significant.

RESULTS

Throughout the experimental period the animals remained well groomed and appeared to maintain normal food and water intake. Vocalization, spontaneous pain behaviors and gait disturbances were not observed after gastrocnemius incision.

Punctate mechanical stimulation

The median withdrawal threshold was 522 mN before and after the sham procedure. Except for a decrease on postoperative day 10 (Fig. 1A, p < 0.05 vs Pre), withdrawal threshold to von Frey filaments remained unchanged after the sham procedure. After skin incision, the median withdrawal threshold decreased from 522 mN to 194 mN 2 h after incision. Withdrawal thresholds were reduced 4 and 6 h after incision and on postoperative days 1, 2, 4, 6, 8, and 14 (p < 0.05 vs Pre, Fig. 1B). Comparison of withdrawal thresholds between rats undergoing skin incision and the sham procedure were different 2 h, 6 h and 1 day after skin incision (p < 0.05 vs sham).

After gastrocnemius incision, the median withdrawal threshold decreased from 522 mN to 89 mN or less from 2 to 6 h; withdrawal thresholds remained decreased for 8 days (p < 0.05 vs Pre) and then gradually returned towards pre-incision values (Fig. 1C). Withdrawal thresholds were significantly reduced for 5 days after gastrocnemius incision and on postoperative day 8 compared with rats undergoing the sham procedure (p < 0.05 vs sham). The withdrawal thresholds after gastrocnemius incision tended to be less than for rats undergoing skin incision; they were not statistically different.

Blunt mechanical and heat stimulation

Because preliminary experiments indicated that responses to the blunt mechanical stimulus and to heat were not increased after gastrocnemius incision, only rats with sham procedure and gastrocnemius incision were studied. Responses to the non-punctate mechanical stimulus applied remote to gastrocnemius incision were not observed (Fig. 2A). There was no difference in withdrawal latency to heat between groups (p > 0.05 vs sham). On occasion, repeated testing reduced the latency compared with baseline (p < 0.05 vs Pre, Fig. 2B).
FIG. 1. Withdrawal thresholds to von Frey filaments. The results are expressed as median (horizontal line) with 1st and 3rd quartiles (boxes), and 10th and 90th percentiles (vertical lines). (A) After sham procedure withdrawal thresholds remained stable. (B) After skin incision, thresholds were reduced through postoperative day 1. (C) Persistent reduced withdrawal thresholds to punctate mechanical stimuli after incision of skin, fascia and muscle of the hindlimb (gastrocnemius incision). (D) The site of incision. The filled circle represents the site of application of the von Frey filaments to the plantar aspect of the hindpaw. *p < 0.05 vs Pre, †p < 0.05 vs sham.

FIG. 2. Lack of response to non-punctate stimulus (A) and heat (B) after gastrocnemius incision. The site of testing and incision is illustrated to the right of the graphs. The symbols represent the mean ± SD. *p < 0.05 vs Pre.
Bupivacaine infiltration and i.t. morphine administration

In incised rats infiltrated with saline vehicle at the hindpaw, the decreased withdrawal threshold after gastrocnemius incision did not change (Fig. 3A). Bupivacaine infiltration 2 h after incision increased the median withdrawal threshold from 41 mN (time 0) to 522 mN 15 and 45 min later (p < 0.05 vs vehicle, Fig. 3B). Bupivacaine infiltration at the test site 2 days after gastrocnemius incision similarly increased the withdrawal threshold (p < 0.05 vs time 0 and vs vehicle, Figs 3C, D). I.t. morphine increased the median withdrawal threshold to 522 mN on the day of incision (p < 0.05 vs vehicle, Figs 4A, B) and on postoperative day 2 (p < 0.05 vs vehicle, Figs 4C, D).

DISCUSSION

In the present study, we report persistent reduced withdrawal thresholds to punctate mechanical stimuli applied remote to an incision in the gastrocnemius region of the rat hindlimb. Threshold reduction was vigorous especially after incision of skin, fascia and muscle. Blockade of the reduced withdrawal threshold after gastrocnemius incision by i.t. morphine indicates that the enhanced withdrawal response is pain-related behavior like the hyperalgesia that occurs remote to incisions in

FIG. 3. Effect of bupivacaine infiltration at the test site on reduced withdrawal thresholds 2 h (A–B) and 2 days (C–D) after gastrocnemius incision. *p < 0.05 vs Pre, †p < 0.05 vs vehicle.

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FIG. 4. Effect of i.t. morphine on withdrawal thresholds 2 h (A–B) and 2 days (C–D) after gastrocnemius incision. *p < 0.05 vs Pre, † p < 0.05 vs vehicle.

postoperative patients. The persistence of the reduced withdrawal thresholds makes the gastrocnemius incision a suitable model for studying mechanisms of secondary hyperalgesia to further understand central sensitization caused by an incision.

Secondary hyperalgesia after incision

We have previously examined the receptive field (RF) expansion of primary afferent fibers 1 day after plantar incision. RF size was estimated by measuring the length and width of the area responding to a suprathreshold punctate mechanical stimulus. The RF size was increased approximately 9-fold and 5-fold in Aδ and C fibers respectively (Pogatzki et al., 2002a). The greatest dimension (length or width) of any afferent RF after incision was 6 mm; therefore, the greatest RF expansion could only have been 6 mm. Because the distance between the site of stimulus application and the incision in the present study (at least 20 mm) was more than the greatest RF length (6 mm), we probably studied secondary hyperalgesia. This was confirmed by bupivacaine injection at the test site.

The absence of secondary heat hyperalgesia after gastrocnemius incision in the present study and after plantar incisions (Zahn and Brennan, 1999b) supports the general finding that reduced heat pain threshold does not occur outside the
zone of injury (Raja et al., 1999). In some pain models (Sluka and Westlund, 1993; Gilchrist et al., 1996; Nozaki-Taguchi and Yaksh, 1998) and in human psychophysical experiments (Arendt-Nielsen et al., 1996; Pedersen and Kehlet, 1998; Serra et al., 1998), secondary heat hyperalgesia has been demonstrated. In human studies, pain magnitude and pain responses to suprathreshold stimuli are greater in the secondary zone. In our studies for secondary heat hyperalgesia, only response latencies were measured. It is possible that response magnitude (e.g., duration of paw licking) or responses to a suprathreshold stimulus may demonstrate secondary heat hyperalgesia. However, a reduction in response latency to heat applied to uninjured areas occurs in some inflammatory pain models (Sluka and Westlund, 1993; Gilchrist et al., 1996; Nozaki-Taguchi and Yaksh, 1998) but not after gastrocnemius incision.

The minimum force required to produce withdrawal in all rats after gastrocnemius incision was always 41 mN or more. Because this is greater than response thresholds of low-threshold mechanoreceptors reported in rats (Lee et al., 1993), behaviors suggesting secondary hyperalgesia after incision may require activation of nociceptors. Similar to secondary hyperalgesia after capsaicin injection, the facilitated pathway is selectively sensitive to punctate mechanical stimuli and is thought to be mediated by Aβ fibers (Ziegler et al., 1999; Treede and Magerl, 2000). The lack of response to a blunt mechanical stimulus after gastrocnemius incision is in agreement with our experiments examining secondary hyperalgesia after plantar incision (Zahn and Brennan, 1999b) and confirms secondary hyperalgesia after incision occurs to punctate mechanical stimuli. It is likely that the blunt stimulus is not of sufficient magnitude because the force is applied over a larger area. In agreement, sharp von Frey filaments produce pain at one-half the force of blunt filaments (Magerl et al., 1998).

In our previous study, secondary hyperalgesia to punctate mechanical stimuli was only modest and not well sustained after plantar incision (Zahn and Brennan, 1999b). Others have reported that the magnitude and duration of secondary hyperalgesia are related to the degree of tissue injury (Gilchrist et al., 1996; Coderre and Katz, 1997; Nozaki-Taguchi and Yaksh, 1998). In the present study, more tissue was injured by the gastrocnemius incision compared with plantar incision. This could explain why the duration of secondary hyperalgesia was greater after gastrocnemius incision. Withdrawal thresholds were also reduced after skin incision that included dissection of the fascia; although no significant differences were evident, withdrawal thresholds after skin incision tended to be greater. This may, again, support the general notion that a greater injury per se causes a greater magnitude and duration of secondary hyperalgesia. Another possible explanation for the more robust hyperalgesia after gastrocnemius incision may be the additional activation of muscle afferents. Afferent fibers originating from muscle tissue produce greater spinal reflex facilitation than activation of cutaneous afferents alone (Wall and Woolf, 1984; Andersen et al., 2000). Therefore the combination of injuries to skin, fascia and muscle may cause vigorous secondary hyperalgesia after gastrocnemius incision.

In experiments by Pitcher et al. (1999), an incision of the upper hindlimb decreased hindpaw withdrawal thresholds to von Frey filaments; threshold reduction was unexpected in this group of rats that received a 'sham surgery' for unilateral sciatic nerve constriction. Withdrawal thresholds were reduced for approximately 40 days after the 'sham surgery' that included incision of the skin, blunt dissection of the biceps femoris muscle and preparation of the sciatic nerve (Pitcher et al., 1999). In the present study secondary hyperalgesia resolved 6 days after gastrocnemius incision. Two factors may account for the differences. To perform a suitable 'sham surgery' for the sciatic nerve injury, Pitcher et al. (1999) included preparation of the sciatic nerve in their surgical procedure. Nerve preparation, which was avoided in the gastrocnemius incision, could have contributed to the nociceptive behaviors in the experiments by others. Also, differences in duration of hyperalgesia in the present study and the one by Pitcher et al. (1999) may be due to differences in the particular muscle that was injured or the methods that were used to assess the withdrawal threshold.
Secondary hyperalgesia in postoperative patients

Secondary mechanical hyperalgesia in most preclinical models usually persists for no more than 24 h (LaMotte et al., 1991; Coderre and Katz, 1997; Petersen and Rowbotham, 1999; Raja et al., 1999). Although the time course of secondary hyperalgesia has not been studied in detail in postoperative patients, a large area of secondary hyperalgesia to von Frey filaments was reported through postoperative day 3 in patients undergoing colectomy (De Kock et al., 2001) and through postoperative day 7 in patients after nephrectomy (Stubhaug et al., 1997). In the present study, the reduced withdrawal threshold was present for 6-8 days after gastrocnemius incision. Because the gastrocnemius incision operates on a similar time scale to secondary hyperalgesia reported after surgery and uses a conditioning injury that is a surgical incision, it is a suitable model for studying mechanisms of enhanced sensitivity to mechanical stimuli remote to a surgical incision in patients.

Mechanisms for secondary hyperalgesia after incision

Evidence suggesting unique mechanisms inherent to incision-induced pain come from neurophysiological experiments. We have found that approximately 40% of Aδ and C fibers have spontaneous activity in rats 1 day after plantar incision (Pogatzki et al., 2002a). None was spontaneously active in the sham group. Ongoing discharge from these activated afferents could enhance transmission at spinal synapses activated by afferent fibers innervating uninjured tissue surrounding the incision as suggested by others (Sandkühler, 2000; Woolf and Salter, 2000).

This would be consistent with our studies recording dorsal horn neurons. After incision, approximately 40% of dorsal horn neurons have sustained increases in background activity (Vandermeulen and Brennan, 2000). A similar proportion developed expanded pinch RFs outside the injured area (Zahn and Brennan, 1999a).

Blockade of afferent input from the incision reversed the increase in background activity and expanded pinch RFs outside the incision area (Pogatzki et al., 2002b). These data indicate that ongoing primary afferent input may be required to maintain central sensitization after incision. Expanded pinch RFs (Zahn and Brennan, 1999a; Vandermeulen and Brennan, 2000) could explain the reduced withdrawal thresholds to stimuli applied remote to the incision in the present study and the large areas of hyperalgesia incorporating uninjured tissue in patients after surgery (Richmond et al., 1993; Tverskoy et al., 1994; Stubhaug et al., 1997; De Kock et al., 2001). The spinal amplification process that leads to secondary hyperalgesia after surgery may have a causative role in clinical perioperative pain by amplifying primary hyperalgesia in the dorsal horn. Central facilitation may also be a factor in the development of persistent or chronic pain after surgery (Perkins and Kehlet, 2000).

CONCLUSION

Secondary hyperalgesia after gastrocnemius incision occurs in response to the same mechanical stimuli causing pain and secondary hyperalgesia in patients after surgery. It is vigorous especially when muscle tissue is incised, has a similar time course to secondary hyperalgesia after surgery in patients and is inhibited by spinal morphine. Future studies using the gastrocnemius incision model will evaluate the etiology of secondary hyperalgesia, its pharmacological characteristics and its role in acute and prolonged pain after surgery.

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REFERENCES


Involvement of N-methyl-D-aspartate receptors in nociception in the cyclophosphamide-induced vesical pain model in the conscious rat

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We previously showed that the intraperitoneal (i.p.) administration of 200 mg/kg cyclophosphamide, an antitumoral agent, modified the behaviour of rats with cystitis induced by acrolein, a toxic urinary by-product of cyclophosphamide. This behaviour, (namely decreased breathing rate, closing of the eyes, and specific postures), was scored to indirectly assess the nociception elicited by the cystitis and to use this experimental model as a vesical pain model. Here we investigated the involvement of the N-methyl-D-aspartate (NMDA) receptors and thus of the excitatory amino acid system in this model.

We administered dizocilpine (0.01 to 0.1 mg/kg intravenously (i.v.) and 1 to 20 μg/rat intrathecal (i.t.)) and ketamine (5 and 10 mg/kg i.v. and 50 to 1000 μg/rat i.t.), two non-competitive NMDA receptor antagonists that bind to the channel site, and AP-5 (0.01 to 1 mg/kg i.v. and 20 to 500 μg/rat i.t.), a competitive antagonist that binds to the glutamate site. Whichever the route of administration (i.v. or i.t.), dizocilpine dose-relatedly reduced the behavioural disorders induced by cyclophosphamide. Systemic ketamine also dose-dependently, though transiently, reduced the effects of cyclophosphamide, but ketamine i.t. and AP-5 i.v. and i.t. did not induce any reduction of these effects.

These results (i) demonstrate that in the cyclophosphamide-induced vesical pain model NMDA receptors are involved in the nociception, as shown by the effects of dizocilpine and systemic ketamine, (ii) reveal marked differences in the data obtained with various NMDA receptor antagonists, possibly due to their physicochemical properties, to the animal pain model used, to the noxious stimulus applied or to any combination of these factors.

Keywords: cyclophosphamide-induced cystitis, nociception, behavioural approach, NMDA receptor, rat.

INTRODUCTION

Excitatory amino acids (EAAs), such as glutamate and aspartate, acting as neuromediators in primary afferent neurones, can act at several different receptors including N-methyl-D-aspartate (NMDA) receptors. These receptors are present at many sites in the central nervous system (Watkins and Evans, 1981; McLennan, 1983) and have been implicated in various mechanisms including in particular nociceptive transmission (Haley et al., 1990). However, it has been suggested that NMDA receptors play an important role in mediating hyperalgesia, but have no effect on nociception under normal
conditions, i.e., in the absence of inflammation and hyperalgesia (Dickenson, 1990; Dubner and Ruda, 1992; Olivar and Laird, 1999; Zhai and Traub, 1999). This has prompted numerous studies of the role of NMDA receptors in nociception (Haley et al., 1990; Davar et al., 1991; Meller et al., 1992; Ren et al., 1992a,b; Yamamoto and Yaksh, 1992; Chaplan et al., 1997), but all these used somatic acute or chronic noxious stimuli. However, in recent years several studies have investigated the possible role of NMDA receptors in hyperalgesia and nociception elicited by damage of internal organs (Cervero, 1994) and particularly in visceral pain. Birder and De Groat (1992) have demonstrated that NMDA receptors at glutamatergic synapses in the spinal cord have a role in processing nociceptive afferent inputs from the lower urinary tract. Subsequently, Kolhekar and Gebhart (1994) showed that NMDA receptor agonists administered intrathecally produced a dose-dependent facilitation of visceromotor together with pressor responses to noxious colorectal distension. Other studies have evidenced that NMDA receptor antagonists inhibit nociceptive responses after visceral nociception (Olivar and Laird, 1999; Zhai and Traub, 1999), thus suggesting that NMDA receptors contribute to visceral nociception and hyperalgesia. In addition, Rice and McMahon (1994), Coutinho et al. (1996) and Ide et al. (1997) have demonstrated that the visceral sensitization produced by inflammation due to turpentine or zymosan is also prevented by NMDA receptor antagonists, suggesting that NMDA receptors may also be involved under inflammatory experimental conditions. Finally, it has been assumed that these NMDA receptors are responsible for central sensitization in the spinal dorsal horn (Ren et al., 1992a) and for the wind-up phenomenon (Dickenson and Sullivan, 1987).

Accordingly, we set out to study the effects of NMDA receptor antagonists on the nociception in cyclophosphamide (CP)-induced cystitis in rats, a recently-developed behavioural model of inflammatory visceral nociception (Lanteri-Minet et al., 1995; Boucher et al., 2000). The latter study has shown that intraperitoneal (i.p.) CP, an antitumoral agent known to produce several toxicity complications including haemorrhagic cystitis of the bladder (Philips et al., 1961; Fraiser et al., 1991), induces marked dose-related behavioural modifications. We therefore investigated the effects of three NMDA receptor antagonists, dizocilpine and ketamine, two non-competitive antagonists that bind to the cationic channel associated with the NMDA receptor/channel complex and block the activation of the NMDA receptor and D-2-amino-5-phosphonovaleric acid (AP-5), a competitive antagonist that binds to the glutamate site (Watkins, 1984; Wong and Kemp, 1991).

METHOD

Animal model and behavioural study

Experiments were performed on male Sprague-Dawley rats (Charles River, St-Aubin-Lès-Elbeuf, France) weighing 220–270 g. The rats were housed six per cage under standard laboratory conditions with free access to food and water. All the experiments were reviewed and approved by the Ethical Committee of the University of Auvergne (registration n°102). As some suffering might result from the experiments, the IASP Committee for Research and Ethical Issues guidelines (Zimmermann, 1983) were followed. In particular, the duration of the experiments was kept as short as possible and the number of rats used was minimized. The experimental conditions have already been described in detail (Boucher et al., 2000). Briefly, i.p. administration of CP 200 mg/kg produced changes in the three behavioural parameters considered, i.e., breathing rate, opening of the eyes, and posture, reflecting the pain felt by the rats. A decrease in breathing rate associated with closing of the eyes, and exhibition of specific postures were observed in rats after CP 200 mg/kg i.p., and these parameters were therefore used as nociceptive indices and scored every 15 mins for 225 mins. Scoring scales were arbitrarily set: a maximum of 10 for each parameter allowing a maximum score of 30 and a minimum of 0, when no parameter was affected. For the breathing rate, every 10 cycles/min decrease was scored 1 with control values of about 140 cycles/min. For the opening of closing
of the eyes, five scale grades were set and scored 0 for complete opening, corresponding to normal eyes, 10 for complete closing, 5 for half-closed eyes and 2 and 7 for the two intermediate positions (between open and half-closed and between half-closed and closed, respectively). Finally, when the specific postures, i.e., either the rounded-back with the whole body aligned or complete limpidness, were observed during the observation period, the score was 10. When no specific posture was seen over the 15-min observation period, the score was 0.

Experimental protocol

All the experiments took place between 8.00 a.m. and 12.00 noon to minimize the potential 24-hour variations in the behavioural responses, and were performed blind, each experimenter scoring up to six rats in parallel. First, to determine the possible involvement of NMDA receptors on this CP-induced cystitis model, the three antagonists of these receptors were intravenously (i.v.) in a caudal vein (0.1 ml/100 g) 90 minutes after i.p. injection of CP 200 mg/kg or saline (1 ml/100 g). Several groups of six rats each were thus formed at random: CP 200 mg/kg i.p. + saline (NaCl 0.9% w/vol) i.v., saline i.p. + dizocilpine 0.1 mg/kg i.v., CP 200 mg/kg i.p. + dizocilpine 0.01 mg/kg i.v., CP 200 mg/kg i.p. + dizocilpine 0.025 mg/kg i.v., CP 200 mg/kg i.p. + dizocilpine 0.05 mg/kg i.v., CP 200 mg/kg i.p. + dizocilpine 0.1 mg/kg i.v.; saline i.p. + ketamine 10 mg/kg i.v., CP 200 mg/kg i.p. + ketamine 5 mg/kg i.v., CP 200 mg/kg i.p. + ketamine 10 mg/kg i.v., saline i.p. + AP-5 1 mg/kg i.v., CP 200 mg/kg i.p. + AP-5 0.01 mg/kg i.v., CP 200 mg/kg i.p. + AP-5 0.1 mg/kg i.v., CP 200 mg/kg i.p. + AP-5 1 mg/kg i.v.

Second, to determine the possible site of the antinociceptive action of these NMDA receptor antagonists, they were administered intrathecally (i.t.) (10 μl/rat) 90 mins after i.p. injection of CP 200 mg/kg or saline. Intrathecal injections consisted in injecting the drug as a volume of 10 μl in the subarachnoid space between L1 and L2 using a 30G needle and a 25 μl Hamilton syringe as described by Mestre et al. (1994), according to a procedure developed by us. Several groups of six rats each were thus formed at random: CP 200 mg/kg i.p. + saline i.t., saline i.p. + dizocilpine 20 μg/rat i.t., CP 200 mg/kg i.p. + dizocilpine 1 μg/rat i.t., CP 200 mg/kg i.p. + dizocilpine 10 μg/rat i.t., CP 200 mg/kg i.p. + dizocilpine 20 μg/rat i.t., saline i.p. + ketamine 1000 μg/rat i.t., CP 200 mg/kg i.p. + ketamine 50 μg/rat i.t., CP 200 mg/kg i.p. + ketamine 500 μg/rat i.t., CP 200 mg/kg i.p. + ketamine 1000 μg/rat i.t., saline i.p. + AP-5 500 μg/rat i.t., CP 200 mg/kg i.p. + AP-5 200 μg/rat i.t., CP 200 mg/kg i.p. + AP-5 250 μg/rat i.t., CP 200 mg/kg i.p. + AP-5 500 μg/rat i.t.

For obvious ethical reasons, all the animals were sacrificed at the end of the experiments with an overdose of sodium pentobarbital.

Drugs

The drugs used were cyclophosphamide purchased from Asia Medica Laboratories (Mégrinac, France), dizocilpine maleate, ketamine hydrochloride and AP-5 from Sigma Chemical Co. (St Louis, Mo, USA) and sodium pentobarbital from Abbott Laboratories (St-Rémy-sur-Arve, France). All the drugs were freshly dissolved in physiological saline, except for CP in distilled water. Doses are expressed in terms of the salt except for CP in terms of base.

Statistical analysis

Results were expressed as arithmetic mean±SEM. For overall comparison of effects observed in the different experimental series, areas under the curves (AUCs) were calculated by plotting individual scores against time. Data were analysed using two-way analysis of variance followed by multiple comparisons using Dunnett's test when the F value was significant. Student's t-test for unpaired samples after comparison of variances was used to compare the effects of two treatments assessed by the AUCs. The statistics software used was StatView 4.5 for Windows p-values < 0.05 were considered statistically significant.

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RESULTS

As shown in the left part of all the figures, CP 200 mg/kg i.p. always produced a strong increase in the behavioural score, resulting from a decrease in breathing rate, closing of the eyes and specific postures, confirming our previous results (Boucher et al., 2000; Mee et al., 2001). When administered in the rats injected with saline i.p., none of the NMDA receptor antagonists used, whichever their route of administration, significantly modified the score, indicating that they did not affect in their own right any of the parameters considered. A reduction of the score during the first 15 mins was observed after the i.t. administration of saline at the L₁–L₂ level in the rats injected with CP 200 mg/kg i.p., which in fact was the result of the i.t. injection itself.

Effects of dizocilpine on the CP-induced behavioural modifications

Dizocilpine at 0.025 to 0.1 mg/kg i.v. significantly reduced the behavioural score of the rats injected with CP 200 mg/kg i.p. (Fig. 1a), indicating that dizocilpine caused a return of the breathing rate to the baseline values, reopening of the eyes and disappearance of the specific postures. This effect, which appeared immediately after injection, was dose-related, as shown by the AUCs, increasing in both intensity and duration, reaching 50% and lasting 60 mins, 76% and 105 mins, and 85% and at least 135 mins at the doses of 0.025, 0.05 and 0.1 mg/kg, respectively.

As shown in Fig. 1b, i.t. administration of dizocilpine at the L₁–L₂ level produced a significant reduction of the behavioural score at 10 and 20 μg/rat in the rats injected with CP 200 mg/kg i.p. At the highest dose of 20 μg/rat this effect reached 77% and lasted at least 135 mins. The AUCs confirm these results.

Effects of ketamine on the CP-induced behavioural modifications

Ketamine at 5 and 10 mg/kg i.v. significantly reduced the behavioural score of the rats injected with CP 200 mg/kg i.p. (Fig. 2a), indicating that ketamine, like dizocilpine, caused a return of the breathing rate to the baseline values, reopening of the eyes and disappearance of the specific postures. This effect, which appeared immediately after injection, increased with the dose as shown by the AUCs, but its pattern appeared quite different from that of dizocilpine with a much shorter duration. Conversely, as shown in Fig. 2b, i.t. administration of ketamine at the L₁–L₂ level at the doses of 50 to 1000 μg/rat did not induce
any reduction of the behavioural score in the rats injected with CP 200 mg/kg i.p.

Effects of AP-5 on the CP-induced behavioural modifications

Whichever the route of administration (i.v. or i.t.) and the doses used (0.01 to 1 mg/kg and 20 to 500 µg/rat), AP-5 did not induce any reduction of the score in the rats injected with CP 200 mg/kg i.p. (Figs 3a and 3b).

DISCUSSION

In conscious rats with CP-induced experimental cystitis, dizocilpine (0.025–0.1 mg/kg i.v.), a non-competitive NMDA receptor antagonist, induced potent dose-related antinociceptive effects. These results obtained using behavioural scoring agree with those of other studies in which dizocilpine significantly attenuated thermal hyperalgesia (Ren et al., 1992a) and mechanical hyperalgesia (Ma et al., 1998; Leem et al., 2001) in rats with unilateral inflamed hindpaw or in a rat model of...
peripheral neuropathic pain (Lee and Yaksh, 1995). This finding also agrees with the results of Birder and de Groat (1992) showing that in rats with an intact spinal cord, dizocilpine administered 15 mins before bladder irritation strongly decreased the number of c-Fos positive cells in all regions of the cord, and with those of Zhai and Traub (1999) demonstrating that dizocilpine produced a dose-dependent attenuation of the noxious colorectal distension-induced spinal c-Fos expression in urethane-anaesthetized rats. Our results thus suggest that the NMDA receptors are probably involved in the vesical nociception resulting from the CP-induced cystitis in the rat. This study also showed that dizocilpine administered i.t. at the dose of 20 μg/rat produced a very strong antinociceptive effect, even more marked than that observed with the highest dose of i.v. dizocilpine, which suggests that the NMDA receptors involved in this effect are located at the spinal site. This is in complete agreement with other studies showing that dizocilpine administered i.t. attenuated thermal hyperalgesia in rats with unilateral inflammation (Ren et al., 1992a,b; Yamamoto et al., 1993) or in a rat model of nerve injury (Yamamoto and Yaksh, 1992; Lee and Yaksh, 1995; Wegert et al., 1997) and reduced formalin nociceptive responses (Coderre and Melzack, 1992), and thus also demonstrating the spinal localization of the NMDA receptors involved in the somatic nociception.

Our results also show that ketamine (5 and 10 mg/kg), a non-competitive NMDA receptor channel blocker, administered systemically induced a relatively short-lasting but marked reduction of the behavioural modifications induced by CP. These results agree with those obtained by Olivar and Laird (1999) demonstrating that the pressor responses to ureter distension were dose-dependently inhibited by ketamine, with a minimum effective dose of 3 mg/kg. For somatic nociception, various studies have demonstrated that ketamine attenuated thermal hyperalgesia after injection of carrageenan (Ren et al., 1992b) or in a rat model of peripheral mononeuropathy (Yamamoto and Yaksh, 1992; Mao et al., 1993). In addition, Haley et al. (1990) have demonstrated that unlike dizocilpine, which produced a long-lasting action, ketamine (1–8 mg/kg i.v.) caused a short-lasting but marked inhibition of the neuronal responses to formalin, which is in perfect agreement with the effects of the two drugs in our pain model. Our results with systemic ketamine confirm NMDA receptor involvement in the processing of nociceptive inputs from viscera, and thus the involvement of the excitatory amino acid system in vesical nociception. However, under our experimental conditions, ketamine administered i.t. (50–1000 μg/rat) did not induce any antinociceptive effect, unlike dizocilpine. These data, which are at variance with some other animal studies, in which ketamine produced an antinociceptive action either in a rat model of mononeuropathy (Yamamoto and Yaksh, 1992; Mao et al., 1993) or after injection of carrageenan (Ren et al., 1992b), can nevertheless be explained by the physicochemical properties of ketamine associated with its short biological half-life. In this experimental vesical pain model, whichever the route of administration (i.v. or i.t.) and the doses used (0.01–1 mg/kg or 20–500 μg/rat), AP-5, a competitive NMDA receptor antagonist, did not induce any antinociceptive action in conscious rats with cystitis. In contrast, other different animal studies using a wide dose range (between 500 ng and 1000 μg) and various experimental pain models have reported data showing that AP-5 i.t. exhibits antinociceptive effects (Dickenson and Sullivan, 1987; Coderre and Melzack, 1992; Ren et al., 1992a,b; Sher et al., 1992; Rice and McMahon, 1994; Ide et al., 1997; Okano et al., 1998). However, our results completely agree with those of Kolhekar and Gebhart (1994), who showed that AP-5 (1 pmol i.t.) did not produce any significant effect on visceromotor and pressor responses to noxious colorectal distension, and of Haley et al. (1990), who report that AP-5 (250 or 500 μg i.t.) had no effect on the electrically evoked C-fibre input. They also report that despite the significant reduction of the response of the neurones to subsequent formalin by the dose of 500 μg, some neurones (5/17) appeared insensitive to AP-5. These data showing the absence of effect of AP-5 and our results on an inflammatory vesical pain model, which remain difficult to explain, suggest that under some
experimental conditions the competitive NMDA receptor antagonist AP-5 is unable to interfere with phenomena involving NMDA receptors.

Overall, our results (i) demonstrate that in the CP-induced vesical pain model NMDA receptors are involved in the nociception, as shown by the effects of dicyclomine and systemic ketamine, (ii) reveal marked differences in the data obtained with various NMDA receptor antagonists, possibly due to their physico-chemical properties, the animal pain model used, the noxious stimulus applied or any combination of these factors.

ACKNOWLEDGEMENTS

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Coping and Quality of Life in relation to headache in Dutch schoolchildren

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The aim of this study was to describe the Quality of Life and pain coping strategies of school children in relation to headache severity. We conducted a cross-sectional study in 2815 children between the age of 9 and 17 years, who filled out the Headache Questionnaire (WHQ), the Paediatric Pain Assessment Tool (PPAT), the Quality of Life Headache in Youth (QLH-Y) questionnaire and the Pain Coping Questionnaire (PCQ) in the class-room setting.

Weekly headaches were reported by 22% of the sample. Low, medium, and high headache severity groups were constructed, based on headache frequency, duration and intensity criteria. Results show that children with the highest headache severity report the lowest Quality of Life in general and the lowest Quality of Health, as well as the most problems with regard to physical functioning, impact of headache on daily and leisure activities, physical symptoms other than headache, and social functioning at home. With regard to using pain coping strategies, children with the most severe headaches seek more social support, they internalize and externalize more, they use less behavioral and cognitive distraction techniques, and seek information less. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Only a few studies so far, have focused on headache-related Quality of Life (QoL). If so, the study population is usually confined to adult migraine sufferers, who report a clearly diminished QoL in comparison to the general population (Michel et al., 1997; Osterhaus et al., 1994), even in between attacks, when they are compared with headache-free controls (Dahlöf and Dimenås 1995). The development of the Quality of Life Headache in Youth (QLH-Y) questionnaire (Langeveld et al., 1996) has provided the impulse to call attention upon QoL in children and adolescents. A study on adolescents with chronic headache and migraine showed that changes in actual headache presence change satisfaction with life in general and satisfaction with health (Langeveld et al., 1997). QoL is a concept that encompasses a broad range of physical and psychological characteristics and limitations that describe an individual’s ability to function, and the satisfaction derived from doing so (Walker and Rosser, 1988). Health-related QoL is affected by physical health, psychological state, level of independence, social relationships, and relationships to salient features of the environment.
The relationship between headache and QoL is complex. We assume a bi-directional relationship, in which headache influences QoL and QoL influences headache. Coping strategies act upon both (Bandell-Hoekstra et al., 2000).

Coping is an intentional cognitive and behavioural effort to manage stress (Lazarus, 1991), with a focus on the problem that causes stress or on emotion-regulation (Lazarus and Folkman, 1984). Children perceive stress as an important trigger of headache (Passchier and Orlebeke, 1985; Bandell-Hoekstra et al., 2001). Assessment of coping strategies to manage stress needs to be the focus of studies aiming at the description of this trigger. However, the headache pain itself can also be viewed as a stressor that needs to be dealt with. Hence, assessment of pain coping strategies needs to be addressed. Children with recurrent headaches mostly prefer taking medication or lying down, to cope with the pain. Moreover, they use distraction, relaxation, seeking social support, problem solving, maintaining a future orientation, remaining positive, wishful thinking and becoming helpless (Spirito et al., 1988).

Since 23% of 10–17 year old school children complain of weekly headaches (Bandell-Hoekstra et al., 2001), focus on recurrent headaches in the general, non-referred population of school-aged children is indicated. Studies on QoL and pain coping in relation to headache in this population are lacking. Aim of the current study was to describe Quality of Life and pain coping strategies in the general population of 9 to 17 year old school children. To this end, we classified the population according to headache severity and compared Quality of Life and pain coping measures of children with low, medium and high headache severity.

**METHODS**

**Subjects and study procedures**

We conducted a cross-sectional study and administered self-report questionnaires to elementary and high school pupils, in the class-room setting. Subjects and sampling methods as well as study procedures have been described elsewhere (Bandell-Hoekstra et al., 2001). School children aged between 9 and 17 years form the population of the current study, which means that with regard to subjects, data of the three highest grades of elementary school were included in the current analysis. Approximately 40% of the children at elementary schools in the City, as well as 20% of the high school pupils in the City and region of Maastricht, have been included.

**Measures**

Assessment of headache severity was based on an adapted version of Waters’ Headache Questionnaire (WHQ) (Waters, 1970; Moss and Waters, 1974; Passchier and Orlebeke, 1985), which was completed with the 0–100 mm Visual Analogue Scale (VAS) on usual and worst pain intensity of the Paediatric Pain Assessment Tool (PPAT) (Abu-Saad, 1984; Huijer Abu-Saad, 1990; Huijer Abu-Saad et al., 1990).

Quality of Life (QoL) was assessed using the Quality of Life Headache in Youth (QLH-Y) questionnaire (Langeveld et al., 1996). The QLH-Y covers two 0–100mm visual analogue scales on QoL in general and Quality of Health, and consists of 69 items comprising 4 subdomains (psychological functioning, physical functioning, social functioning and functional status). The subscales that encompass the subdomains of the QLH-Y (see Table 3) were more or less confirmed by principal component factor analysis using oblique rotation. Cronbach’s alphas were between 0.77 and 0.97. After a pilot-study on the length and difficulty of the questionnaires, the wording of a few items of the QLH-Y were simplified.

Pain coping was assessed using the Pain Coping Questionnaire (PCQ) (Reid et al., 1998). The 39 items cover 8 subscales, concerning information seeking, problem solving, seeking social support, positive self-statements, behavioural distraction, cognitive distraction, externalizing and internalizing or catastrophizing. The PCQ was translated into Dutch using the forward–backward method. Factor analysis of the PCQ (maximum likelihood procedure using
TABLE 4. Mean and 95% confidence intervals of QLH-Y sub-domains presented by low, medium and high headache severity group. Negative scores have been recorded, i.e. high scores mean high QL.

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Quality of Life</td>
<td>76 (74–78)</td>
<td>71 (70–72)</td>
<td>67 (64–70)</td>
</tr>
<tr>
<td>Quality of Health</td>
<td>76 (74–78)</td>
<td>66 (66–69)</td>
<td>55 (56–63)</td>
</tr>
<tr>
<td>Psychological</td>
<td>63.24 (62.60–63.87)</td>
<td>61.06 (60.61–61.48)</td>
<td>55.44 (54.50–56.38)</td>
</tr>
<tr>
<td>Functional status*</td>
<td>40.34 (40.00–40.69)</td>
<td>39.77 (39.55–39.96)</td>
<td>36.78 (36.35–39.21)</td>
</tr>
<tr>
<td>Physical symptoms</td>
<td>25.89 (25.41–25.77)</td>
<td>25.15 (25.03–25.26)</td>
<td>23.67 (23.30–24.03)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>10.95 (10.50–11.36)</td>
<td>10.17 (9.91–10.44)</td>
<td>9.48 (8.89–10.06)</td>
</tr>
</tbody>
</table>

* Subjects without headache in the week previous to completion of the QLH-Y were excluded from analysis on this sub-domain

TABLE 5. Mean and 95% confidence intervals of PCQ subscales presented by low, medium and high headache severity group.

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem solving</td>
<td>1.90 (1.83–1.96)</td>
<td>2.07 (2.03–2.11)</td>
<td>2.21 (2.11–2.31)</td>
</tr>
<tr>
<td>Information seeking</td>
<td>2.90 (2.86–3.36)</td>
<td>2.69 (2.64–2.74)</td>
<td>2.36 (2.26–2.48)</td>
</tr>
<tr>
<td>Positive self-statement</td>
<td>1.26 (2.20–2.36)</td>
<td>1.36 (2.20–2.30)</td>
<td>1.59 (2.04–2.23)</td>
</tr>
<tr>
<td>Seeking social support</td>
<td>1.87 (1.81–1.94)</td>
<td>2.07 (2.02–2.11)</td>
<td>2.22 (2.13–2.31)</td>
</tr>
<tr>
<td>Cognitive distraction</td>
<td>2.50 (2.52–2.98)</td>
<td>2.69 (2.64–2.74)</td>
<td>2.36 (2.26–2.48)</td>
</tr>
<tr>
<td>Behavioral distraction</td>
<td>2.54 (2.47–2.61)</td>
<td>2.30 (2.20–2.34)</td>
<td>2.09 (2.00–2.16)</td>
</tr>
<tr>
<td>Internalizing</td>
<td>1.50 (1.45–1.54)</td>
<td>1.78 (1.75–1.82)</td>
<td>2.34 (2.24–2.44)</td>
</tr>
<tr>
<td>Externalizing</td>
<td>1.28 (1.24–1.32)</td>
<td>1.38 (1.33–1.39)</td>
<td>1.59 (1.51–1.67)</td>
</tr>
</tbody>
</table>

headache. Children in the low headache severity group experience the highest Quality of Life and children in the medium headache severity group report Quality of Life scores in between. When compared to the low headache severity group, social functioning is lower in the medium as well as the high headache severity group.

Pain coping strategies

Results of the differences between the low, medium, and high headache severity groups in using pain coping strategies for dealing with headache, are reported in Table 5. All three groups differ in seeking social support, using behavioural distraction and cognitive distraction, internalizing/catastrophizing and externalizing. A higher headache severity means seeking social support more, but using less distraction techniques and more catastrophizing and externalizing. There is no difference between the three groups in using positive self-statements. Children in the medium and high headache severity group use more problem solving strategies than children with low headache severity. Children in the high headache severity group use less information seeking strategies.

DISCUSSION

Headache severity and QoL were found to be negatively related. Children with at least weekly headaches with a mean duration of more than an hour and a mean pain intensity of at least 50 mm on a 0–100 mm VAS, experience the lowest QoL in all sub-domains. They report the lowest QoL in general and the lowest QoH, and rate their psychological functioning, functional status, and physical symptoms other than headache worse than children with medium or low headache severity. Children with medium and high headache severity equally rated their social functioning worse than children with low headache severity. Within the sub-domain psychological functioning, children with the highest headache severity specifically experienced more stress, less harmony and vitality, more fatigue, and more depression.
Headache severity is related to the use or disuse of coping strategies. Children with the most severe headaches seek more social support, by talking to someone about how they feel. They internalize and externalize more. Internalizing means that they worry more and keep on thinking about the pain, and that it will never stop. Externalizing means that they express their hurt by yelling, cursing or getting mad or mean. They use less behavioural and cognitive distraction techniques, such as doing something funny or active, or trying not to think about it. They also seek information (asking questions about the headache) less.

Before drawing conclusions, several features of our study design need to be discussed. First of all, the cross-sectional nature of our study does not permit to draw firm conclusions about the direction or the causality of the relationships, between headache severity and QoL, headache severity and pain coping strategies, and pain coping and QoL. More severe headaches may influence QoL. But a low score on elements of QoL, such as stress, depression, and difficulties with regard to social functioning, may contribute to headache problems as well. A more prospective study design in adolescents, showed that a high score on experienced stress increases the impact of headache on psychological functioning and satisfaction with life (Langeveld et al., 1999). Pain coping strategies may be influenced by previous pain experiences, parental coping and actions towards the child, role modeling, perceived pain cause, self-efficacy and so on (Bandell-Hoekstra et al., 2000). In addition, pain coping strategies have an impact on pain severity. Good or healthy pain coping strategies, however, are difficult to distinguish from bad coping and are determined by individual differences, type of pain and underlying disease, nature of the pain (i.e., acute, chronic), the distinction between coping style (trait) and specific coping strategies (state), and short-term adjustment and long-term effects (Reid et al. 1998). In addition, the influence of person-specific and situation-specific variables on headache, pain coping and QoL still needs to be unravelled. A literature overview and a conceptual model on headache, coping, QoL and influencing variables has recently been published (Bandell-Hoekstra et al., 2000). Second, the QLH-Y and PCQ both focus on patient populations. The QLH-Y has been developed for adolescents with chronic headaches or migraine. It is, however, a generic QoL measurement scale, in which only the subscale 'functional status' refers to headache. Item reduction and factor analysis was conducted in a sample of healthy school children (Langeveld et al., 1997). The inclusion of younger children in our study did not result in problems with construct validity. The PCQ shows different higher order factor structures within a healthy population, and within a sample of children with recurrent pain, including headache (Reid et al., 1998). The Danish translation of the PCQ, tested within healthy children, resulted in 7 subscales instead of 8 (Thastum et al., 1998). More studies on the PCQ, including a broad international range to allow for cultural and translation differences, are thus warranted.

Third, we focused on primary headaches using headache severity as a classification method, instead of focusing on a well-defined population of migraine and/or tension-type headache patients. Our approach sheds light on the total problem of headache in school children, but studies on specific patient populations are needed as well.

We conclude with stressing the importance of QoL, and the challenge of pain coping, in studies on paediatric headache. Children with the highest headache severity score significantly lower on Quality of Life, compared to their peers with less severe headaches, and they use pain coping strategies differently. This confirms the need for studies on headache treatment in children.

We need to know more about QoL and pain coping strategies in relation to headache. Prospective studies would provide more information about the direction of relationships. In addition, QoL and pain coping strategies should not only be included in assessment studies but in treatment studies as well.

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EFIC was formed by the Presidents of the European Chapters of the International Association for the Study of Pain (IASP) at a meeting held during the 7th World Congress on Pain in Paris in August 1993.

Aims

These are in general those of IASP, i.e. to promote research, education and the clinical management of pain. The specific aim is to create a forum for European collaboration on pain issues and to encourage communication at a European level between IASP Chapters, and also with other bodies interested or involved in the fields of pain research and therapy such as the European Societies or Federations of Medical Specialties (anaesthesiology, neurology, headache, palliative care etc.), institutions of the European Community, European and national educators and legislators.

Constitution

The affairs of EFIC are conducted by its Council, which consists of the Presidents of the European IASP Chapters, and five elected officers who form the Executive Committee. The Council meets once a year while the Committee manages affairs between meetings. EFIC is being established as a charitable foundation in Belgium.

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EFIC’s Position in Relation to IASP

The bylaws of the IASP (section V) provide that national pain societies and associations may constitute Chapters of the IASP in their country. EFIC acts as a European grouping of these, so that they will benefit from the wider perspectives offered by a transnational organization while allowing for the sociocultural diversity of European nations and regions. Many of the societies have a large percentage of members who are not members of the IASP; they are nonetheless members of EFIC and will benefit from the wider perspectives offered by a transnational organization.

Specific Programmes

EFIC co-operates in the organization of Congresses, such as that in Verona, Italy, in May 1995 and that in Barcelona, Spain, in September 1997. It produces newsletter which is distributed by the Chapters to all their members and is involved with the production of the European Journal of Pain. Under its auspices, task forces are working on aspects of pain research and management, and their findings will be used to improve education and training throughout Europe.

Further information about EFIC can be obtained from Sarah Wheeler, EFIC Executive Secretary, Ponton 59, 17675, Athens, Greece.
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