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Effect of Prolonged Nerve Block on Inflammatory Hyperalgesia in Rats

Prevention of Late Hyperalgesia

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Background: **Recent evidence suggests that the duration of the nociceptive block may be an important factor in determining the effect of the block on injury-induced hyperalgesia after block resolution. The authors examined whether a tonicaine nerve block lasting for 12 to 16 h could prevent late inflammatory hyperalgesia.**

Methods: **Inflammatory hyperalgesia was induced by injection of carrageenan into the rat paw. A threshold of motor response to increasing pressure was determined for the injected paw, contralateral paw, and tail. The development of edema of the paw and an increase in paw temperature also were determined. The block was achieved by simultaneous percutaneous injections of tonicaine (a new long-acting anesthetic agent) or lidocaine at the sciatic nerve (greater trochanter level) and the saphenous nerve (midthigh level).**

Results: **Carrageenan without nerve block caused a profound primary (injected paw) and secondary (contralateral paw and tail) hyperalgesia that lasted for 3–5 days. Tonicaine nerve block administered before carrageenan completely prevented primary and secondary hyperalgesia. Tonicaine block administered 5 h after carrageenan injection reversed secondary hyperalgesia and prevented the development of late (≥ 24 h) primary and secondary hyperalgesia. Edema and temperature of the paw were not significantly affected by the nerve block administered before or after carrageenan.**

Conclusions: **A prolonged nerve block (12–16 h) can prevent the development of long-lasting (3–5 days) inflammatory hyperalgesia. Prevention of late hyperalgesia can be provided not only by the preinjury block but also by the postinjury block administered when hyperalgesia is already well established. (Key words: Acute postoperative pain; carrageenan inflammation; lidocaine; tonicaine.)**

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CONTROVERSY persists regarding the clinical significance of preemptive analgesia.[1,2] As we suggested previously,[3] the most important factor in this controversy is that the concept of prevention of postoperative pain involves two phenomena: (1) Antinociceptive treatment started before surgery is more effective in the reduction of postoperative pain than treatment given on recovery from general anesthesia (phenomenon of preemptive analgesia in a narrow sense); and (2) the effective blockade of noxious stimuli generated during surgery and during the initial postoperative period (inflammatory phase) reduces subsequent postoperative pain (phenomenon of preemptive analgesia in the broad sense).

Laboratory analysis of the role of preemptive analgesia in the broad sense requires two conditions: models of nociceptive input of long duration and nerve blocks that provide protection against nociceptive input for a sufficient time interval. In their recent study, Fletcher *et al.*[4] used the carrageenan model of hyperalgesia, which has a time course (3–5 days) close to that of postoperative pain. They found that infiltration of bupivacaine into the paw, which provides a direct analgesic effect for ≈2–2.5 h, revealed no significant preemptive effect; the difference between animals receiving bupivacaine 5 min before or 60 min after carrageenan was not evident after infiltration anesthesia wore off. The authors concluded that their block may have been too short to reveal a preemptive analgesic effect. Pederson *et al.*,[5] experimenting with mechanical hyperalgesia after thermal injury in volunteers, reported that a nerve

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block lasting 8–9 h reduced late postburn primary and secondary hyperalgesia beyond the duration of the block.

We hypothesize that, if the afferent block is prolonged and complete, the preemptive analgesic effect (in the broad sense) should be pronounced, even with nociceptive input lasting several days. To test this, we used a model of carrageenan hyperalgesia with an approach similar to that of Fletcher *et al.*[4] Instead of infiltration of bupivacaine into the paw, however, we used a nerve block with tonicaine[6] that provided a long-lasting local anesthetic effect.

Methods

Experiments were performed on male Sprague-Dawley rats weighing 225–275 g. The animals were housed with a 12-h light–dark cycle, and food and water were available *ad libitum*. The protocol for this study was approved by the Institutional Panel on Laboratory Animal Care.

Inflammation was induced by injection of 0.1 ml of 2% carrageenan (Sigma Chemical, St. Louis, MO) subcutaneously (30-gauge needle) in the plantar surface of the hind paw under halothane (2%) anesthesia. Hyperalgesia was determined by measuring the threshold of motor response (coordinated struggle) to increasing pressure[7–9] with the use of an Analgesy-Meter (Ugo Basile, Milan, Italy). Primary hyperalgesia (changes in sensation within the area of injury) was determined in the inflamed paw by positioning the paw on a Teflon platform and directing the device's 2-mm pressure cone on its dorsal surface. Secondary hyperalgesia (changes outside the injury) was determined as threshold changes in the contralateral paw and the tail. The pressure on the tail was applied with a pressure plate (0.7-mm edge) attached to the Analgesi-Meter. The cutoff pressure was 300 g for the paw thresholds and 600 g for the tail threshold. Animals received training sessions with measurement of the motor response to increasing pressure, two on a day before the drug injections and one before the actual baseline measurement.

To evaluate the edema, the plantar circumference of the injected paw was measured by a thread at the metatarsal level as described by Fletcher *et al.*[4] The paw temperature was measured with a thermocouple thermometer (Yellow Spring Instrument, Yellow Spring, OH) applied for 15 s to the plantar surface of the paw.

The blockade of the nociceptive input from the inflamed paw was achieved by percutaneous injections of a local anesthetic at two nerves, the sciatic and saphenous. Both nerves were blocked simultaneously (under brief halothane anesthesia), the sciatic nerve at the greater trochanter level (as described by Thalhammer *et al.*[10]) and the saphenous nerve at midthigh level. For a prolonged blockade, tonicaine (20 mM in 5% dextrose and 5% glycerol) was injected in a volume of 0.2 ml at the sciatic nerve and 0.1 ml at the saphenous nerve. Preliminary experiments demonstrated that the mean ± SD duration of the block was 11.2 ± 1.2 h (n = 6) for recovery of the withdrawal reflex to deep pinch of the fist (saphenous nerve) and the fifth (sciatic nerve) toe; the motor threshold to increasing pressure returned to the preblock level in 13.8 ± 2.3 h (n = 6). For comparison, a lidocaine block was also used. Lidocaine was administered as a 37-mM (1%) solution in saline providing the blockade for 0.5–1.0 h.

The animals were randomly assigned to one of the following groups (n = 8 per group). In the group 1, the precarrageenan tonicaine block (TC) group, tonicaine was injected after baseline measurements, and the completeness of sciatic and saphenous nerve blockade was confirmed 10 min later by toe pinch. Immediately after this, carrageenan was administered, and all variables were measured at 3, 5, 24, 48, and 72 h and then every second day for another 4–6 days. In the group 2, the postcarrageenan tonicaine block (CT) group, carrageenan was injected first, and 5 h later (after the 3- and 5-h measurements of all variables), the tonicaine blockade was provided. The rest of the measurements were the same as in the first group. Groups 3 through 6 served as controls. In group 3, the intramuscular tonicaine (no block) with carrageenan (imTC) group, tonicaine (20 mM, 0.2 ml, and 0.1 ml) was injected in thoracolumbar paraspinal muscles (two sites) 10 min before carrageenan injection into the paw. In group 4, the tonicaine block without carrageenan (T) group, sciatic and saphenous nerves blocks were provided without injection of carrageenan. Group 5 received lidocaine block before carrageenan (LC). The lidocaine blockade of the sciatic and saphenous nerves was provided 10 min before the injection of carrageenan in the paw. The sixth group received carrageenan without nerve block (C). Measurements were made by an experimenter who did not know of expected changes in the reaction thresholds among the group with paw inflammation.

Statistical Analysis

Raw data were expressed in grams for the motor reaction threshold to pressure, in millimeters for the paw circumference, and in degrees Celsius for paw temperature and are presented as mean ± SD. They were analyzed using a two-way (group and time) analysis of variance, with time treated as a repeated-measures factor.[11] Comparisons between groups at each time were per-

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formed with one-way analysis of variance.[12] Multiple comparisons among means were made using Fisher's protected least-squares difference test.[12] The results were declared significant if $P < 0.05$.

Results

The results in the groups in which inflammation was induced without the nerve block (C and imTC) demonstrated that, by the fifth hour after carrageenan injection, the motor reaction threshold to pressure on the inflamed paw decreased by approximately half (*e.g.*, in the C group, from 138 ± 10 g to 65 ± 19 g). Twenty-four hours after the carrageenan injection, the motor threshold in this group was decreased to a somewhat lesser degree: 87 ± 21 g. The process of the threshold recovery was gradual and continued for ≈7 days. The motor reaction threshold to pressure on the hind paw contralateral to an inflamed paw and on the tail also was decreased, revealing the remote secondary hyperalgesia. In the C group, the contralateral paw threshold decreased from 139 ± 12 to 113 ± 12 g at 5 h and to 113 ± 16 g 24 h after the carrageenan injection; the tail threshold decreased from 382 ± 18 to 302 ± 23 g at 5 h and 301 ± 23 g 24 h after injection. Changes in the motor reaction threshold in the imTC group were not substantially different from those in the C group.

The comparison between the imTC control group and the groups with tonicaine blocks administered before (TC) or after (CT) carrageenan is summarized in figure 1. Late (≥ 24 h) hyperalgesia in the inflamed paw was prevented by tonicaine nerve block administered before the injection of carrageenan, and the changes in the motor reaction threshold in the group with tonicaine block administered 5 h after carrageenan were not different from those in the group with precarrageenan block. The 24- and 48-h changes of the motor reaction thresholds in all groups are presented in figure 2, which demonstrates that late (24 and 48 h) primary hyperalgesia was present almost at identical levels (30–35% decreases from baseline) in the C, imTC, and LC groups and was practically absent in the TC and CT groups. Therefore, precarrageenan long-lasting (12–16 h) tonicaine block in contrast to short (0.5–1.0 h) lidocaine block was effective in preventing late hyperalgesia. The postcarrageenan block also prevented the development of late primary hyperalgesia well beyond the block resolution (fig. 1A).

When the tonicaine block was administered without the carrageenan injection, no significant changes were noted in the motor reaction threshold after recovery from the direct local anesthetic effect at 24 h and during a 3–7 day period, but at 48 h a small but statistically significant ($P < 0.05$) decline was noted in the threshold of the paw with the block (fig. 2A).

The results with secondary hyperalgesia (contralateral hind paw and tail) were similar to those with primary hyperalgesia (figs. 1B and 2B). The late changes in the motor reaction thresholds in both the TC and CT groups were absent or minimal (compared with the imTC, C, and LC groups; fig. 2B). For example, the contralateral paw threshold in the C group decreased from 139 ± 12 to 113 ± 16 g at 24 h (−19%; $P < 0.001$) and to 116 ± 12 g (−16%; $P < 0.001$) at 48 h. At the same time, in the TC group the contralateral threshold value was not changed. In the CT group, minimal changes were noted in the motor reaction threshold only at 48 h. The contralateral paw threshold at 48 h decreased from 148 ± 12 (baseline) to 136 ± 7 g (−8%; $P < 0.05$) and, for the tail, from 414 ± 32 (baseline) to 388 ± 21 g (−6%; $P < 0.01$). These changes were significantly smaller than those in the C group, however ($P < 0.05$; fig. 2B).

Changes in circumference and temperature of the paw caused by carrageenan were maximal 5 h after injection. The paw circumference increased from baseline by ≈30–35%. For example, in the C group, it increased from 29.9 ± 0.6 to 41.0 ± 1.6 mm ($P < 0.0001$). The paw temperature in the same group increased 5 h after the carrageenan injection from 28.7 ± 1.3 to 32.3 ± 0.5°C ($P < 0.0001$). Twenty-four hours after injection, both the paw circumference and the temperature reduced by approximately one fourth compared with 5-h values; after this time, there were daily gradual decreases in the carrageenan-induced changes that lasted for more than a week. Evolution of the paw circumference and of the paw temperature in the imTC, TC, and CT groups is illustrated in figures 1C and 1D. The results demonstrate that these two indices of inflammation were not influenced by the tonicaine block administered before or after carrageenan injection. Lidocaine block was also ineffective in this respect. Five hours after carrageenan injection, the paw circumference in the LC group was 40.5 ± 1.3 mm, and the temperature was 31.8 ± 0.7°C, which are almost identical to the values in the C group. The variables at the other time intervals also indicated no significant changes compared with control.

Discussion

The carrageenan model of inflammation used in our study resulted in changes in paw circumference and

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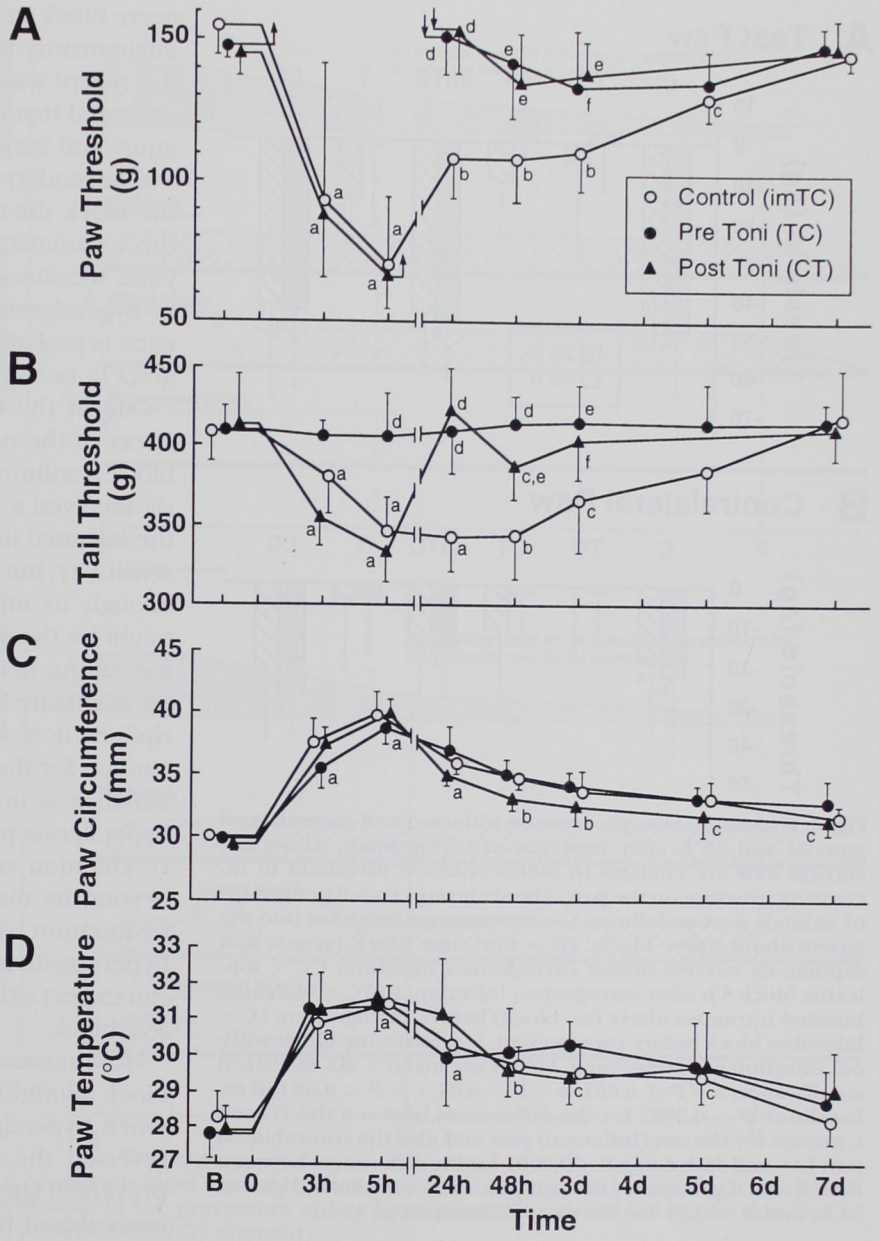

Fig. 1. The effects of tonicaine nerve block administered before (Pre Toni) or 5 h after (Post Toni) injection of carrageenan into the paw *(A)* on the threshold of response to paw pressure, *(B)* on the threshold of response to tail pressure, *(C)* on the edema of the paw, and *(D)* on the temperature of the paw. Values are mean ± SD; n = 8 per group. B = baseline; O = injection of carrageenan; imTC = tonicaine injected intramuscularly (no block) before carrageenan (control); TC = tonicaine block (sciatic and saphenous nerves) before carrageenan; CT = tonicaine nerve block 5 h after carrageenan. Statistical significance: a = $P < 0.0001$, b = $P < 0.001$, c = $P < 0.01$ (all *vs.* baseline); and d = $P < 0.0001$, e = $P < 0.001$, f = $P < 0.05$ (all *vs.* control; imTC group).

reaction threshold to pressure similar to those observed by Fletcher *et al.*[4]; these authors reported that, 4 h after carrageenan injection, paw circumference increased by 41% and vocalization threshold to the pressure on the inflamed paw decreased by 55%. In our study, 5 h after the injection of carrageenan, the paw circumference increased by 37% and the motor reaction threshold to pressure decreased by 40%. The degree of change in the threshold was only slightly reduced at 24 and 48 h; it gradually returned to baseline level by the 7th–9th day. Also, changes in motor reaction threshold to pressure on the contralateral paw and the tail, reflecting the degree of secondary hyperalgesia, were significant (decrease of the thresholds by 15–20%) and lasted almost as long as changes in the injured paw. These findings agree with the results on distant secondary hyperalgesia caused by the paw injury.[13–16]

Our results demonstrate that carrageenan-induced primary and secondary hyperalgesia lasting up to 3–5 days was prevented by preinjury block with tonicaine, which

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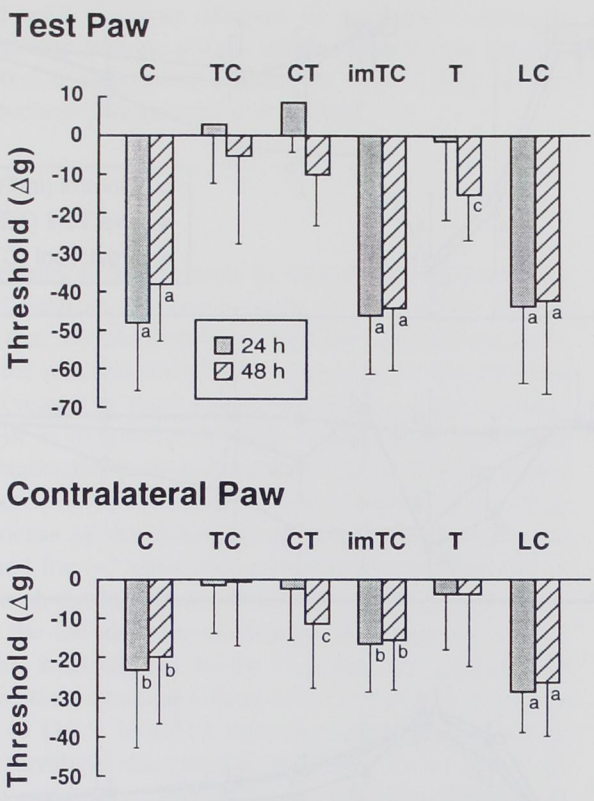

Fig. 2. Hyperalgesia to pressure on inflamed and contralateral paw 24 and 48 h after injection of carrageenan. Along the vertical axis are changes in motor reaction threshold to increasing pressure on the paw. The six groups (n = 8 per group) of animals were as follows: C = carrageenan injection into the paw without nerve block; TC = tonicaine block (sciatic and saphenous nerves) before carrageenan injection; CT = tonicaine block 5 h after carrageenan injection; imTC = tonicaine injected intramuscularly (no block) before carrageenan; LC = lidocaine block before carrageenan; T = tonicaine block without injection of carrageenan. Values are mean ± SD. Statistical significance: a = $P < 0.001$, b = $P < 0.01$, c = $P < 0.05$ (all *vs.* baseline); $P < 0.0001$ for the differences between the TC and C groups for the test (inflamed) paw and also the contralateral paw (24- and 48-h data); $P < 0.0001$ for the differences between the CT and C groups for the test paw and contralateral paw at 24 h; and $P < 0.01$ for the same differences at 48 h.

provided a direct local anesthetic effect for 12–16 h. At the same time, short-term (0.5–1 h) nerve block with lidocaine produced no significant changes in carrageenan-induced hyperalgesia. Fletcher *et al.*,[4] using carrageenan-induced inflammation and infiltration of bupivacaine into the paw, found no significant preemptive effect of infiltration. Carrageenan-induced primary hyperalgesia reappeared in their experiments immediately after the infiltration anesthesia (lasting for 2–2.5 h) wore off; this finding agrees with the suggestion that the nerve block should be sufficiently prolonged to prevent inflammatory hyperalgesia. The important indication in this regard was presented by Pedersen *et al.*,[5] who demonstrated that nerve block administered before thermal injury and lasting 8–9 h reduced late postburn primary and secondary hyperalgesia for several hours beyond the block duration. In our experiments, the effect on the inflammatory hyperalgesia lasted several days beyond the duration of the block, and the development of hyperalgesia was completely prevented. The difference is probably due to the different nature of hyperalgesia in our model of inflammation.

One of the explanations for the persistence of the effect of the nociceptive block far beyond the time of block resolution might be that our model of hyperalgesia involved a long period when a noxious input from the inflamed tissues was able to maintain central hypersensitivity, but at the same time the input was not strong enough to initiate the hypersensitivity. The process might be the same as that suggested by Gracely *et al.*[17] for painful neuropathy: Altered central processing can be maintained for a long time by a relatively weak peripheral noxious input. If the preinjury block lasts long enough for the noxious input to decline to the level at which it is unable to initiate central hypersensitivity, hyperalgesia prevention will be permanent (fig. 3, part I). Duration of the preventive effect of the blockade beyond its direct pharmacologic effect is determined by duration of afferent input that can maintain central hypersensitivity. If this period is very prolonged, one can expect a significant clinical advantage of the preventive block.

Most interesting were the results with tonicaine nerve block administered 5 h after the carrageenan injection when hyperalgesia was already established. The block reversed the established secondary hyperalgesia and prevented late (≥ 24 h) primary and secondary hyperalgesia almost to the same extent as the precarrageenan tonicaine block.

Several groups of authors studied the effect of local anesthetic blockade on an established secondary hyperalgesia. Some observed no changes,[13,18] whereas others reported a pronounced effect with a rapid return of hyperalgesia after block resolution[16,19,20] or partial hyperalgesia reduction.[21] Only Levine *et al.*[14] observed complete and permanent reversal of secondary hyperalgesia; however, in their experiments, blockade of the sciatic and saphenous nerves with lidocaine was followed by section of the nerves. Differences between intensity and duration of nociceptive input causing hy-

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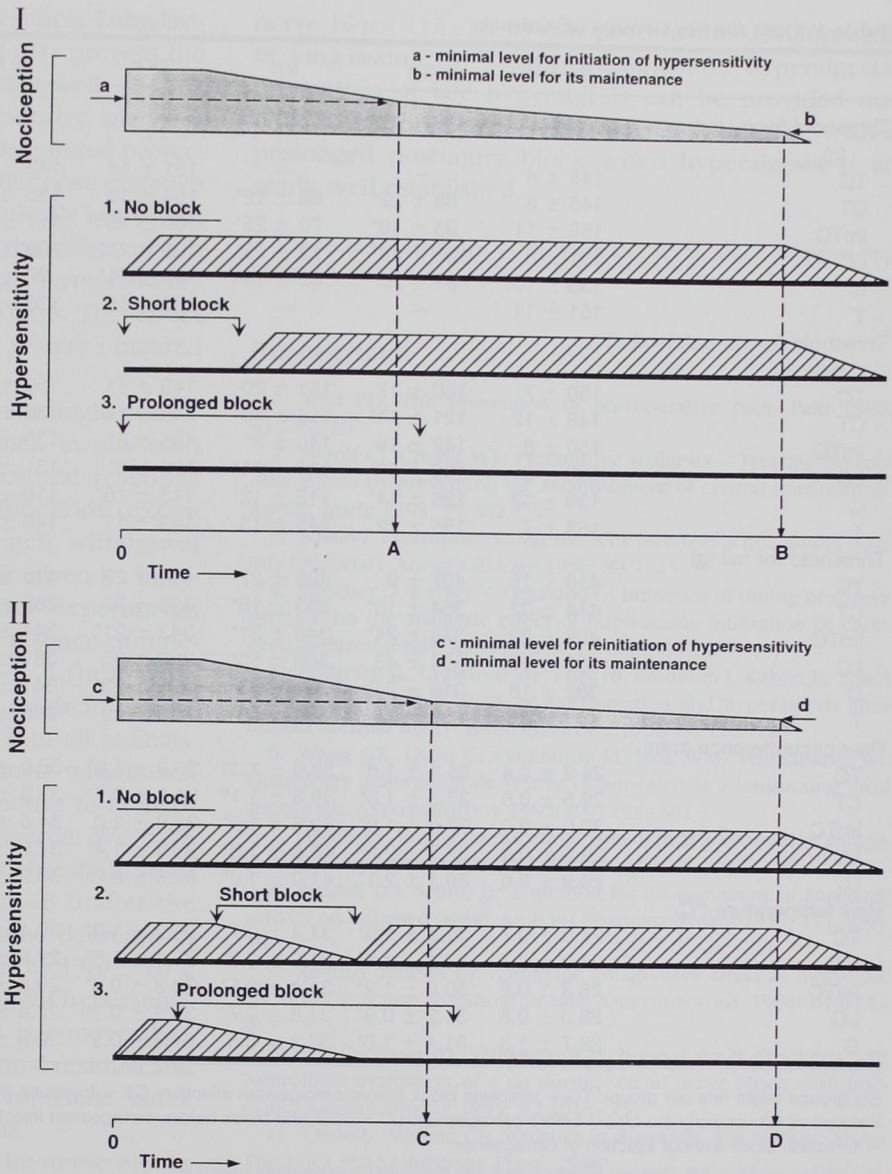

Fig. 3. A model illustrating hypothetical conditions necessary to prevent late hyperalgesia. The upper panels in each figure part represent a nociceptive input caused by the injury and inflammatory response to the damaged tissue. The lower panels represent three possible variants of the central hypersensitivity states generated in response to the afferent input with different block conditions: no block (1), short block (2), and prolonged block (3) *(part I)* Preinjury block. a = a minimal level of the nociceptive input necessary for initiation of the state of central hypersensitivity; b = a minimal level of the nociceptive input necessary to maintain the state of central hypersensitivity. The segment on the horizontal axis between A and B represents the time interval when the nociceptive input is unable to initiate the state of central hypersensitivity but yet strong enough to maintain it. If a preinjury block lasts beyond point A, hyperalgesia prevention will be permanent; the clinical significance of this effect is determined by the duration of afferent input that potentially can maintain hypersensitivity (AB segment). If a preinjury nerve block does not reach point A (short block) the peripheral afferent input will be strong enough to initiate central sensitization. *(part II)* Postinjury block. c = a minimal level of the nociceptive input necessary to reinitiate the state of central hypersensitivity (note that it is lower than level a in the part of fig. 3I that is necessary to initiate central hypersensitivity). There are two conditions for permanent prevention of late hyperalgesia when a block is administered with established central hypersensitivity. One condition (peripheral) is that the blockade should last until the intensity of a noxious input below the level that could potentially reinitiate central hypersensitivity (beyond the C point on the time axis). The other condition (central) is that the established hypersensitivity in the absence of afferent input caused by the block should disappear before block resolution. As in the case of preinjury block, clinical significance of the prevention of late hyperalgesia is determined by the duration of afferent input that potentially can maintain hypersensitivity (CD segment).

peralgesia on the one hand and completeness and duration of the nerve block on the other was probably the reason for the discrepancies between results reported by these authors.

Hypothetical conditions that determine effectiveness of the block with established hyperalgesia are presented in figure 3, part II. One condition is that the blockade should last until the intensity of a noxious input from the inflamed tissues decreases below the level that could potentially reinitiate central hypersensitivity (peripheral condition). The other condition (central) is that the established hypersensitivity in the absence of afferent input should subside and disappear before block resolution. The intensity of noxious input for reinitiation of central hypersensitivity should probably be lower than that for its initiation (compare levels a and c in fig. 3). In the carrageenan model of hyperalgesia, the 12–16 h blockade probably was sufficient to satisfy both the central and peripheral requirements for permanent reversal of hyperalgesia. The duration of the bene-

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Table 1. Data for Six Groups of Animals

	Baseline	3 h	5 h	24 h	48 h	3 days	5 days	7 days
Threshold for tested paw (g)								
TC	148 ± 4	—	—	151 ± 14	143 ± 20	134 ± 21	135 ± 12	149 ± 7
CT	145 ± 8	88 ± 22*	66 ± 12*	154 ± 15	135 ± 17	139 ± 11	—	148 ± 10
imTC	155 ± 11	93 ± 49*	70 ± 25*	109 ± 15*	111 ± 16*	112 ± 15*	130 ± 8*	145 ± 5
LC	151 ± 8	103 ± 28*	73 ± 25*	108 ± 21*	109 ± 23*	125 ± 22*	121 ± 16*	145 ± 13
C	138 ± 10	81 ± 25*	65 ± 19*	87 ± 21*	97 ± 14*	112 ± 18*	—	124 ± 12
T	151 ± 11	—	—	150 ± 15	136 ± 16*	141 ± 21	144 ± 17	145 ± 9
Threshold for contralateral paw (g)								
TC	150 ± 7	160 ± 17	151 ± 20	148 ± 11	150 ± 15	138 ± 13	144 ± 17	148 ± 5
CT	148 ± 12	121 ± 11*	118 ± 10*	145 ± 14	136 ± 7*	141 ± 11	152 ± 7	148 ± 9
imTC	150 ± 8	142 ± 18	140 ± 8*	135 ± 8*	133 ± 10*	135 ± 13*	141 ± 6	143 ± 7
LC	158 ± 9	135 ± 15*	134 ± 21*	129 ± 8*	131 ± 16*	143 ± 10*	129 ± 8*	149 ± 16
C	139 ± 12	126 ± 14*	113 ± 12*	113 ± 16*	116 ± 12*	115 ± 12*	—	126 ± 10
T	153 ± 7	156 ± 12	145 ± 13	149 ± 11	149 ± 12	146 ± 7	143 ± 10	149 ± 10
Threshold for tail (g)								
TC	410 ± 15	407 ± 9	406 ± 27	411 ± 28	415 ± 18	416 ± 23	415 ± 25	417 ± 13
CT	414 ± 32	354 ± 18*	333 ± 18*	423 ± 27	388 ± 21*	404 ± 25	—	411 ± 20
imTC	409 ± 20	378 ± 24*	346 ± 21*	343 ± 21*	344 ± 27*	367 ± 33*	385 ± 26	418 ± 33
LC	400 ± 20	394 ± 43	360 ± 53*	380 ± 35	381 ± 41	363 ± 29*	386 ± 43	393 ± 30
C	382 ± 18	318 ± 24*	302 ± 23*	301 ± 23*	341 ± 36*	366 ± 23	—	370 ± 25
T	408 ± 21	399 ± 34	396 ± 18	408 ± 29	386 ± 37	390 ± 9	406 ± 21	416 ± 17
Paw circumference (mm)								
TC	29.9 ± 0.4	35.4 ± 1.6*	38.6 ± 1.3*	36.9 ± 1.9*	35.0 ± 1.1*	34.0 ± 1.1*	33.1 ± 1.0*	32.8 ± 1.7*
CT	29.5 ± 0.5	37.3 ± 1.3*	39.8 ± 1.1*	34.8 ± 0.7*	33.0 ± 0.9*	32.4 ± 1.4*	31.7 ± 1.6*	31.3 ± 1.0*
imTC	30.0 ± 0.0	37.5 ± 1.9*	39.6 ± 1.9*	35.9 ± 1.0	34.6 ± 0.9*	33.6 ± 1.6*	33.0 ± 1.3*	31.5 ± 0.9
LC	29.9 ± 0.4	37.5 ± 2.0*	40.5 ± 1.3*	35.4 ± 1.4*	34.6 ± 1.2*	33.4 ± 1.2*	32.1 ± 1.7*	31.3 ± 0.7
C	29.9 ± 0.6	39.1 ± 2.1*	41.0 ± 1.6*	37.8 ± 2.0*	36.2 ± 1.5*	35.3 ± 2.1*	34.5 ± 2.1*	33.2 ± 1.5*
Paw temperature (°C)								
TC	27.8 ± 0.7	31.3 ± 1.0*	31.4 ± 0.7*	29.9 ± 1.3*	30.1 ± 1.2*	30.3 ± 0.7	29.7 ± 1.2*	28.7 ± 0.9
CT	27.9 ± 0.7	31.2 ± 1.1*	31.6 ± 0.8*	31.1 ± 1.6*	29.6 ± 0.7*	29.4 ± 0.7*	29.7 ± 1.5*	29.0 ± 1.1
imTC	28.3 ± 0.8	30.9 ± 1.2*	31.4 ± 0.5*	30.3 ± 0.8*	29.8 ± 0.5*	29.5 ± 0.8*	29.4 ± 0.7*	28.2 ± 0.7
LC	28.0 ± 0.8	31.2 ± 0.9*	31.8 ± 0.7*	30.3 ± 0.7*	29.4 ± 0.9*	29.6 ± 0.8*	28.7 ± 0.7	28.5 ± 1.4
C	28.7 ± 1.3	31.4 ± 1.0*	32.3 ± 0.5*	31.3 ± 0.5*	30.8 ± 0.9*	29.9 ± 1.2*	29.0 ± 0.6	27.9 ± 0.7

Six groups (eight rats per group): TC = tonicaine block before carrageenan injection; CT = tonicaine block 5 h after carrageenan injection; imTC = tonicaine injected intramuscularly (no block) before carrageenan; LC = lidocaine block before carrageenan injection; C = carrageenan injection without nerve block; T = tonicaine block without injection of carrageenan.

Values are mean ± SD. Column headings indicate time after carrageenan injection.

* Significantly different from baseline ($P < 0.05$).

ficial effect of the block beyond block resolution is determined, as with the preinjury nerve block, by the duration of afferent input that could potentially maintain central hyperexcitability.

The lack of clinically important differences between the outcomes of preinjury and postinjury analgesic treatments is well known.[22,23] Woolf and Chong[2] suggested that one of the reasons for this lack of difference is the reinitiation of central sensitization after completion of surgery. It seems likely that only preemptive analgesia in the broad sense, which also includes treatment during the initial postoperative period, can demonstrate a clinically important effect[3] (for reviews on differences in assessment of the value of preemptive analgesia see refs. 2, 22, and 23). With the carrageenan model of hyperalgesia, we demonstrated only very small differences in secondary hyperalgesia between preinjury and postinjury administration of tonicaine block that did not even reach a statistically significant level ($P < 0.08$ at 48 h; fig. 1). The duration of the block should probably be shorter for a more significant difference. Our results suggest a reason for the absence of

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preinjury *versus* postinjury block difference: Long-lasting block provided by both treatments may prevent the development of late hyperalgesia equally well.

Usually only clinical studies on preemptive analgesia in the broad sense, when a relatively prolonged protective effect extended well into the initial postoperative period, were able to demonstrate a clinically important effect.[24-27] In one of these studies,[27] the effect of 9-h neural blockage given before inguinal herniorrhaphy reduced late hyperalgesia for up to 10 days. This effect observed in patients is similar to the results obtained in the current study.

Wang *et al.*[6] Performed a complete neurologic evaluation of the tonicaine sciatic nerve block in rats with evaluation of resting posture, gait, postural reactions (hopping and tactile placing), motor functions (extensor postural thrust), and heat and pinch withdrawal responses. They reported that tonicaine given by injection in a manner similar to that in our experiments completely blocked all functions. The absence of functions lasted from 3-4 h (motor) to 6-7 h (heat withdrawal). All the functions evaluated in their experiments completely recovered in 9-24 h in all animals. In our experiments, in addition to pinch withdrawal responses, the threshold of motor response to increasing pressure on the paw was also measured. We have observed recovery of the injected paw threshold from the tonicaine block in 13.8 ± 23 h. In 48 h after the tonicaine injection, there was even some decrease in the threshold from 151 ± 11 (baseline) to 136 ± 16 g (−9%; $P < 0.05$), perhaps indicating a slight hypersensitivity after long-lasting nerve block. It is conceivable, although we believe unlikely, that potential residual and selective nerve damage produced by tonicaine block could contribute to the obtained results.

We detected no significant effect of the nerve blocks on the indices of carrageenan-induced paw inflammation. Fletcher *et al.*[4] obtained similar results; 240 min after carrageenan administration, the paw circumference and the temperature of the paw were similar to those of the control and block groups. A tendency for a reduced incidence of blister formation after thermal injury in legs with a preemptive nerve block was reported by Pedersen *et al.*[5] Another index of inflammation used in their study, erythema intensity, was not changed by the block, however. Diminished neurogenic inflammation is, in principle, a possible result of nerve block[28]; however, it was not a substantial factor for changes of hyperalgesia observed in our study.

The experiments demonstrated that a prolonged nerve block (12-16 h) can prevent the development of long-lasting (3-5 days) inflammatory hyperalgesia. Prevention of late hyperalgesia can be provided not only with a prolonged preinjury block but also with a prolonged postinjury block when hyperalgesia is already well established.

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