Thermal Hyperalgesia Accelerates and MK-801 Prevents the Development of Tachyphylaxis to Rat Sciatic Nerve Blockade

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Background: Tachyphylaxis to local anesthetics has been shown to be promoted by longer interanalgesic intervals between injections. We hypothesized that thermal hyperalgesia also would accelerate the development of tachyphylaxis. The n-methyl-D-aspartate antagonist ((+)-5 methyl-10,11-dihydro-5H-dibenzo(a,d) cyclohepten-5,10-imine, or dizocilpine) (MK-801) has been shown to prevent thermal hyperalgesia. We therefore also hypothesized that MK-801 would prevent tachyphylaxis.

Methods: Catheters were surgically implanted in rats along the sciatic nerve. After recovery and conditioning to the testing paradigm, they received repeated injections of lidocaine or 2-chloroprocaine followed by motor block testing with or without hot-plate testing at 48, 52, or 56°C. In other experiments, MK-801 or saline was administered by intraperitoneal injection before sciatic nerve local anesthetic injection and sensory and motor testing.

Results: Rats receiving repeated lidocaine or 2-chloroprocaine injections, when repeatedly subjected to hot-plate testing at 56°C, developed thermal hyperalgesia and tachyphylaxis to motor and sensory blockade. Rats receiving either no hot-plate exposure or hot-plate exposure at 48°C did not exhibit tachyphylaxis or hyperalgesia. Rats tested at 52°C developed milder hyperalgesia and developed tachyphylaxis more slowly than did rats tested at 56°C. Control experiments excluded artifacts due to circadian rhythm, injection volume, and learning. Rats pretreated with MK-801 showed no tachyphylaxis over a series of three injections.

Conclusions: Thermal hyperalgesia accelerates the development of tachyphylaxis to rat sciatic nerve blockade, and MK-801 prevents tachyphylaxis in this model. n-Methyl-D-aspartate receptor antagonists may have future clinical utility in increasing the duration of effectiveness of prolonged local anesthetic administration. (Key words: Anesthesia; local. Antagonists, n-methyl-D-aspartate; MK-801. Pain: hyperalgesia. Receptors: n-methyl-D-aspartate. Tachyphylaxis.)

TACHYPHYLAXIS to local anesthetics has been described by clinicians over the past 25 years. Bromage noted that repeated injection of a constant dose of epidural lidocaine led to a reduction in both the number of dermatomes blocked and in the duration of blockade.1 Tachyphylaxis has been described for both ester and amide linked local anesthetics. It reportedly occurs with short acting agents such as 2-chloroprocaine as well as long acting agents such as bupivacaine.2,3 Tachyphylaxis has been described during both neuraxial blocks1,4,5 and peripheral nerve blocks.2 The rate of development of tachyphylaxis appears quite variable. We reported previously on a patient who developed tachyphylaxis slowly over three months on two occasions.6

Bromage found that the development of tachyphylaxis depended on the interanalgesic interval. If local anesthetic injections were repeated at intervals short enough to prevent return of pain, or to permit pain for no more than 10 min, then tachyphylaxis did not occur. Conversely, if the patient was permitted to experience longer periods of discomfort, tachyphylaxis occurred more rapidly.1

Baker and colleagues developed a rat model for studying tachyphylaxis involving repeated injections via a catheter with a sleeve around the sciatic nerve.2 They found that repeated injections of bupivacaine produced a small but significant decrement in the duration of motor blockade with incomplete recovery on successive days. Sensory blockade was not measured.

Based on our previous inability to demonstrate tachyphylaxis in the regulation of cation flux through sodium channels in cell culture7 and on Lipfert et al’s8 inability to show tachyphylaxis in the compound action poten-
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tial in isolated nerve preparations, coupled with Bromage's observations regarding the acceleration of tachyphyllaxis with unrelieved pain, we hypothesized that the development of tachyphyllaxis may be related to changes in the intact nervous system's responses to injury, possibly related to the behavioral phenomenon of hyperalgesia or the electrophysiologic phenomenon of "wind-up." Many forms of injury or inflammation have been shown to produce subsequent increases in the excitability of dorsal horn neurons.

We modified Baker's model of tachyphyllaxis to rat sciatic nerve blockade to include sensory and motor testing. We tested whether protocols that produce thermal hyperalgesia by repeated foot pad application to the hot plate accelerate the development of tachyphyllaxis. In addition, we examined whether tachyphyllaxis and hyperalgesia could be prevented simultaneously by pretreatment with (+)-5 methyl-10,11-dihydro-5H-dibenzo (a,d) cyclohepten-5,10-imine, or dizocilpine) (MK-801), a noncompetitive antagonist at the n-methyl-D-aspartate (NMDA) receptor.

Materials and Methods

All procedures were approved by the institutional review board for animal care. Male Sprague-Dawley rats, 300–500 grams in weight were studied.

Catheter Implantation

Tachyphyllaxis was studied using a modification of the technique described by Baker and colleagues. A catheter was placed with its tip near the sciatic nerve to allow repeated application of local anesthetic without repeatedly subjecting the rat to distressing procedures. The catheter was produced by inserting a 22-G Quik-cath intravenous catheter (Travenol Laboratories, Deerfield, IL) into a length of 0.030-inch inner diameter silicone elastomere tubing (Silastic tubing, Dow Corning, Midland, MI). The catheter assembly was sterilized by incubation in 95% ethanol for at least 10 min. Before insertion, the catheter was flushed with three volumes of sterile antibiotic solution to prevent neuroysis resulting from the alcohol. An occluding heparin lock cap with male Luer lock (CCI, Orrville, OH) was placed onto the Quik-cath to maintain sterility. The cap was secured to the Quick-cath with dental cement. (fig. 1).

The catheter was placed as shown in figure 1. General anesthesia was induced and maintained with halothane 2–2.5% in oxygen delivered via nose cone. A midline incision was made between the scapulae, and a subcutaneous pocket bluntly dissected. A second skin incision was made over the sciatic nerve, which was localized by bisecting a line from the greater trochanter of the femur and the posterior iliac spine. The gluteal muscles were split in the direction of their fibers and retracted to expose a pocket containing the sciatic nerve. A catheter tunneller was then passed between the two incisions. The flushed and capped catheter was passed through the tunneller from the cephalad incision caudad and a redundant loop was loosely sutured to the gluteal fascia (fig. 1A). The wings of the Quik-cath were sewn to the fascia overlying the paraspinous muscles to secure the catheter and the skin was closed around the catheter, leaving the injection port exteriorized. When the entire catheter was placed subcutaneously in preliminary experiments, the repeated injections through the skin rendered the rats less cooperative. The distal end of the catheter was tunneled through the gluteal muscles, trimmed to an appropriate length and anchored to the fascia such that the catheter lay parallel to and less than five millimeters away from the nerve (fig. 1B). The nerve itself was not manipulated in order to prevent any artifact from neuronal damage. The side of the catheter was alternated on successive rats. After closing the muscular pocket, the
catheter was flushed with 0.5 ml of antibiotic solution. The skin was then closed with a running subcuticular suture. Before awakening the rat, acetaminophen (Tylenol drops, 80 mg/0.8 ml) 20 mg/kg was administered per rectum to minimize postoperative discomfort. The rats were then given 100% oxygen to breathe until fully awake, and returned to their cages. There was no perioperative mortality with this anesthesia protocol and no postoperative wound infections at either incision. After catheter placement the rats were allowed to recover overnight.

**Sensory Testing**

The hot-plate test was modified as described by Masters and colleagues. In brief, a uniformly heated hot plate (3D Analgesy Meter, IITC, Life Scientific, Woodland Hills, CA) was brought to the desired temperature, initially 56°C. The rat was wrapped in a towel leaving its hind legs free. The rat was then held so that one hind foot was resting on the hot plate and the other was resting on a block of wood at room temperature. The time from placing the rat onto the hot plate to lifting of the foot was recorded. To prevent the rat from sustaining injury to the foot in the event of a dense block, if the rat did not lift the foot by 12 s the investigator removed the rat from the hot plate and scored a result of 12 s. The responses of the rat’s feet were tested alternately with a 15-s rest period between each test. Each foot was tested five times at each time point. The middle three values were averaged and referred to as the hot plate latency time for the time period designated by the beginning of the testing period. Thus the value designated “0 min” was collected from the time of injection over approximately 5 min, etc. The rats were tested on the hot plate for several days with saline injections through the catheters until the hot-plate latency was reproducible and equal bilaterally. When sensory testing was performed using a 52°C hot plate, the average baseline latency was 6.9 ± 0.56 s. As this was more than half of the 12-s cutoff we had been using for the 56°C hot-plate test, we increased our cutoff to 15 s at 52°C and 48°C. None of the rats used in these experiments developed any inflammation, edema, blistering of the feet or had any other physical signs of thermal injury in response to hot-plate testing during this protocol.

**Motor Testing**

Three motor tests were used, following recent work by Thalhammer et al.†

**Motor Strength Test.** The rat was held over an electronic balance (OHaus, Florham Park, NJ) to which was taped a gauze pad. The rat was lowered such that one hind paw was allowed to grip the gauze. Increasing pressure was then applied to cause the rat to lay the entire foot, including the heel flat against the surface of the scale. The force in grams required was recorded.

**Postural Reactions. Tactile Placing.** The rat’s hind paw was dorsiﬂexed. The response was recorded as either positive if the foot was immediately returned to a normal position or negative if not done within 5 s.

**Hopping Response.** The rat is held over a foam mat such that one hind leg is bearing some of the rat’s weight and the other three paws are off the table. The rat is then moved sideways such that the weight bearing paw is adducted. The normal response of the rat is to hop. The rat with a sciatic nerve block will allow the affected foot to drag. This response was graded 1 for no hopping through 4 for normal hopping.

This set of tests requires less than 30 s to complete for each rat, but provides a broad assessment of motor capability in natural movements and proprioception.

The duration of neural blockade was assessed by injecting 1 ml/kg of local anesthetic through the sciatic nerve catheter and then testing hot-plate latency or motor function every 10 min until the blocked paw returned to the control value. This always occurred within 90 min after the injection of 3% 2-chloroprocaine or 2% lidocaine. Duration of block was measured as the time to recovery by 50% from full block toward baseline in the sensory and motor strength tests, and by duration of abnormal response in tactile placing and hopping response tests. Tachyphylaxis, defined as a decreased duration of effect from the same dose of local anesthetic, was assessed by performing three injections, 2 h apart, and measuring recovery times after each injection.

**Testing Protocols**

**Effects of Repeated Sciatic Nerve Blockade with Local Anesthetics.** Rats prepared with a sciatic catheter and previously adapted to the restraint and testing paradigm were tested using the hot plate at 56°C at −10 min, immediately after injection (0 min), 10 min, 20 min, and so on until the response returned to or below baseline for that nerve block. This cycle was repeated three times at 2-h intervals, measured from


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Fig. 2. Time course of hot-plate latency after injection of 3% 2-chloroprocaine in a single rat over several days. Squares = first injection of the day; diamonds = second injection of the day; triangles = third injection of the day. Tachyphylaxis developed, seen as decreased durations of sensory and motor block after identical injections of local anesthetic.

the start of the first block to the start of the next. In the later experiments, motor testing was also performed at each time point. Each rat received sciatic nerve injections of vehicle (saline 1 ml/kg), 2-chloroprocaine (1 ml/kg of 3%), or lidocaine (1 ml/kg of 2%).

Effect of Temperature. To define the effect of test temperature in the development of tachyphylaxis, rats were trained and tested as in protocol 1, except that the test temperature was varied. Additional hot-plate temperatures tested were 52°C and 48°C. Rats were also tested using the motor test only without hot-plate sensory testing.

Effect of MK-801. To test the effect of MK-801 on the development of tachyphylaxis in this system, MK-801, 0.1 mg/kg was injected intraperitoneally twice daily. In separate groups of rats, the morning dose was given 1 or 2 h before the start of sensory testing. Initial testing of timing of MK-801 on the prevention of tachyphylaxis showed no difference between the groups so the data were merged in the results. The evening dose was given after the completion of all testing for the day, between 5:00 and 6:00 PM. Control rats were given intraperitoneal injections of 0.3 ml saline. The dosing schedule for MK-801 was based on previous work using MK-801 to prevent morphine tolerance.

Effect of Volume. One possible trivial explanation for the apparent development of tachyphylaxis in this system is that the volume of injectate distends a tissue plane, opening up a pocket around the sciatic nerve. Thus subsequent injections might have a decreased effect because less local anesthetic contacts the nerve. The pocket could then collapse down overnight, allowing the first block to be equal in duration to that of the previous day. We tested this hypothesis by injecting saline 1 ml/kg into the sciatic nerve catheter at 2-h intervals four times, then performing a block with 3%, 2-chloroprocaine 1 ml/kg at the final (fifth) injection. This was compared to rats receiving a nerve block using 3% 2-chloroprocaine 1 ml/kg for the first injection of the day.

Effect of Circadian Rhythm. To exclude changes in block duration due to circadian rhythm, testing was started either in the morning with the first nerve block started between 0700 and 0900, or in the afternoon with the first block started between 1300 and 1500.

Pharmaceutical Preparations

MK-801 was obtained from Research Biochemicals Incorporated, (Natick, MA). It was dissolved in sterile water and brought to pH 7.4 ± 0.2 with NaOH. Aliquots containing 0.05 mg, 0.1 mg/kg, in 0.3 ml were then frozen in 1-ml syringes for later use in the experiments demonstrating reversal of tachyphylaxis.

Fig. 3. Time course of sensory and motor block after injections of 3% 2-chloroprocaine with 56°C hot-plate testing. (A) Hot-plate latency and (B) motor strength test measured in the same animals. Points are means ± standard deviation; n = 5 rats. Squares = first injection; diamonds = second injection; triangles = third injection. Tachyphylaxis developed, seen as decreased durations of sensory and motor blocks after identical injections of local anesthetic.
Lidocaine 2% (Xylocaine) and 2-chloroprocaine 3% (Nesacaine) were obtained from Astra Pharmaceuticals (Westborough, MA) in 30-ml vials.

**Statistical Methods**

Pairwise comparison of blocks was performed using two-factor analysis of variance with repeated measures. Comparison of block duration and baseline hot-plate latency values between subsequent blocks on the same animals was performed using a paired two-tailed t test. Comparison of block duration between different groups of animals was performed using unpaired two-tailed t tests. All statistics were performed using the statistical package in Excel 4 (Microsoft, Redmond, WA). A P value of 0.05 was considered statistically significant.

**Results**

**Development of Tachyphylaxis**

Rats treated with repeated sensory testing at 56°C consistently developed tachyphylaxis to motor and sensory blockade with both 2-chloroprocaine and lidocaine. Figure 2 shows the repeated development of tachyphylaxis to 2-chloroprocaine in a single rat over several consecutive days. The duration of the sciatic nerve block is measured with hot-plate testing at 56°C. The first block on each day was of the same duration, indicating that there was complete recovery from tachyphylaxis by the next morning in each case. Average values of hot-plate latencies measured at 56°C after repeated sciatic injections of 2-chloroprocaine 30 mg/kg are graphed in figure 3A. Tachyphylaxis, a decrease in the duration of the block, developed. There was marked development of tachyphylaxis over the course of 6 h; duration of blockade was significantly different between the first and second and between the second and third blocks at the P = 0.05 level and between the first and third blocks at P < 0.001.

The development of tachyphylaxis to the motor strength test when the rats were concurrently tested with the 56°C hot plate is shown in figure 3B. This measurement also demonstrates that the block durations were different at the P < 0.05 significance level for all pairings. Mean times to 50% recovery from the block for three consecutive blocks were 72, 50, and 32 min respectively measured by sensory testing (P < 0.05 between any pair). As measured by motor strength test, the mean times to 50% recovery were 65, 37, and 25 min (P < 0.05 between any pair). Thus motor block
tended to recover more quickly than sensory block for any block, but the trends were parallel for the different types of tests. Results of the tactile placement test and hopping response also paralleled the above results (table, first column).

Figure 4 demonstrates that similar tachyphylaxis developed to hot-plate testing at 56°C when lidocaine was used as the local anesthetic ($P < 0.05$ between any pair of blocks).

**Effect of Hot-plate Temperature on the Development of Tachyphylaxis**

Figure 5A shows the development of tachyphylaxis to sciatric nerve block with 2-chloroprocaine as measured by sensory testing with the 52°C hot plate. Times to 50% recovery from the sensory block were 60, 58.3, and 50.8 min for the first, second, and third blocks, respectively. There were significant differences between the second and third, and between the first and third blocks, but not between the first and second blocks ($P < 0.05$). Concurrent motor testing of these animals is shown in figure 5B. Times to 50% recovery of motor function were 63.3, 57.5, and 53.3 min for the first, second, and third blocks, respectively. There was a significant difference between the first and second, and first and third blocks, but not between the second and third ($P < 0.05$). Thus tachyphylaxis developed when sensory testing was performed with a 52°C hot plate but not as rapidly as when a 56°C hot-plate test was used.

When the rats were tested using a hot plate at 48°C, they did not lift either foot off the hot plate for 15 s on any test throughout the entire day of testing. The rats also did not develop tachyphylaxis to sciatric nerve block as measured by motor testing when concurrent 48°C hot-plate testing was performed ($P > 0.25$ between the first and third blocks) (fig. 6). When the experiment was repeated with motor but no hot-plate testing, again no tachyphylaxis developed (fig. 7) ($P > 0.8$). Table 1 summarizes the effect of testing temperature on tachyphylaxis.

**Effect of Thermal Hyperalgesia on the Development of Tachyphylaxis**

After frequent hot-plate testing for the duration of the sciatric nerve block, the rats demonstrated hyperalgesia to thermal stimuli once the block had worn off. For rats tested with a 56°C hot plate (fig. 3), the average baseline hot-plate latency at the start of the first nerve block of the day averaged 3.6 ± 0.3 s. The average latency at the start of the second block of the day averaged 2.6 ± 0.3 s and at the start of the third block

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of the day averaged 2.3 ± 0.2 s, a decrease of 36% from the latency before the first block. Thus the thermal hyperalgesia caused by the hot-plate testing was partially sustained during the intertesting interval. By the following morning, however, the baseline hot-plate latency and the duration of the first block of the day had returned to their initial values. Similarly, at 52°C, the hot-plate latency decreased over the course of a single day of testing from 6.9 ± 0.5 s at the start of the first block to 5.8 ± 0.5 s at the start of the third (n = 4 rats; P < 0.05). This is a decrease in latency of 16%. By the following morning it had recovered completely, averaging 6.7 ± 0.9 s at the start of the first block of the 2nd day (n = 4 rats; P > 0.5, not significant). With only motor testing or hot-plate testing at 48°C neither thermal hyperalgesia nor tachyphylaxis developed.

Figure 8 correlates percentage decrease in duration of subsequent sciatic nerve blocks from 2-chloroprocaine with the percentage decrease in the baseline hot-plate latency measured before the injection of local anesthetic. The baseline hot-plate latency for subsequent blocks decreased from that of the first block of the day because of thermal hyperalgesia. A similar effect occurs with lidocaine (not shown). The development of tachyphylaxis was dependent on the development of hyperalgesia from the hot-plate testing.

**Effect of MK-801 on Tachyphylaxis**

Intraperitoneal administration of MK-801 prevented the development of tachyphylaxis in this model (figs. 9 and 10). MK-801 also prevented the development of thermal hyperalgesia in the blocked hindpaw despite repeated hot-plate exposure at 56°C. The baseline hot-plate latencies for the first and third blocks were 3.4 ± 0.6 and 3.3 ± 0.4 s respectively for the MK-801 treated rats (P = n.s.), whereas they were 3.9 ± 0.3 and 3.3 ± 0.4 s in the control rats (P < 0.01).

MK-801 even in tenfold higher doses had no significant effect on baseline hot-plate latency. In a separate
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Fig. 9. Duration of sensory block after injection of 2-chloroprocaine with or without intraperitoneal MK-801. Block duration was defined as the time required for hot-plate latency at 56°C to return 50% of the way from maximal block toward baseline. MK-801 was given intraperitoneally, 0.1 mg/kg every 12 h starting 36 h before the experiment. Points are means ± standard deviation; n = 7 rats in each set.

In rats did not occur over the course of three injections in rats that were not hyperalgesic; (2) tachyphylaxis proceeded rapidly in animals rendered hyperalgesic by the effects of repeated 12 s exposures to 56°C hot plate while numb; and (3) the NMDA antagonist-801 prevented development of tachyphylaxis. The alternative explanation, that the rat is not becoming tachyphylactic, but rather is simply avoiding touching the hyperalgesic plantar surface of his paw is ruled out by the tactile placing test, which does not require that the rat touch the plantar surface of his foot at all. Tachyphylaxis to the motor strength test precisely parallels development of tachyphylaxis to the tactile placing test. Control experiments further excluded trivial alternative explanations for these observations, including effects of injectate volume, circadian rhythm and systemic effects of the local anesthetics or MK-801.

Despite the wide variety of clinical experiences suggesting that tachyphylaxis may occur during neural blockade with local anesthetics, there is surprisingly little known about underlying mechanisms. Several models have been suggested: alternative possibilities are that there is a pharmacokinetic change with an increase in drug clearance from the site of action with prolonged exposure or that there is a pharmacodynamic change such that the target nerve or whole organism is more resistant to the effects of local anesthetics. Evidence for either of these proposals has been limited.

Baker and colleagues have shown that pH of the local anesthetic does not influence the onset of tachyphylaxis. Mogensen demonstrated that with the onset of experiment, baseline hot-plate latency of control rats were 3.5 ± 0.6 s, and the baseline hot-plate latency of rats treated with MK-801 0.5 mg/kg averaged 3.0 ± 0.6 s (P not significant).

**Effect of Volume of Injectate**

As a control for repeated volumes distending a tissue space, rats received four injections of normal saline at 2-h intervals followed by a fifth injection of 2-chloroprocaine. The mean time to 50% recovery from this block was 54 ± 16.7 min (mean ± standard deviation). The mean time to 50% recovery of the initial block of the day for these same rats on the following day was 60 ± 21.2 min (P not significant).

**Effect of Circadian Rhythm**

Croquet and colleagues found that mice exhibit slight diurnal variation in their latency of withdrawal to a 59°C hot plate. To evaluate the effect of circadian rhythm on the development of tachyphylaxis, we started the experiment at different times of the day. When comparing experiments in which the first block was performed between 7:00 and 9:00 am with those in which the first block was performed between 1:00 and 5:00 pm, there was no statistically significant difference in the duration of the first block or in the percentage decrement between the first and second or first and third blocks.

**Discussion**

These studies indicate that (1) tachyphylaxis to sciatic nerve blockade with lidocaine or 2-chloroprocaine

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clinical tachyphylaxis, there is no difference in the spread of local anesthetic in the epidural space or clearance of lidocaine from the epidural space. In a live animal preparation, Lipfert and colleagues studied the propagation of compound action potentials through rabbit sciatic nerve partially blocked with several concentrations of local anesthetics. They found either no change or an increasing intensity of block over a 4-h exposure period. In vitro studies have not led to a convenient tachyphylaxis model. Our group has attempted to produce tachyphylaxis to chronic exposure to lidocaine, tetrodotoxin, or veratridine in neuronal cell cultures with exposure periods of 5–14 days. Under a wide range of conditions, there was no modification in the basal or maximally activated cation flux through either tetrodotoxin-sensitive or tetrodotoxin-resistant sodium channels, and subsequent responses to local anesthetic blockade of the flux were identical between chronic drug treated cells and control cells.

Pharmacologic prevention or treatment of hyperalgesia has been of recent interest, both to aid in understanding the molecular and electrophysiologic events underlying hyperalgesia and wind-up, and because of the possibility that this will lead to improved drug therapy of many forms of acute and chronic pain, including neuropathic pain. There has been considerable interest in the role of excitatory amino acid transmitters released by primary sensory neurons at termini in the dorsal horn. In particular, the action of glutamate on NMDA receptors is thought to be significantly involved in the development of wind-up and hyperalgesia. Blockade of the NMDA receptor by intrathecal administration of the antagonist MK-801 in rats prevented thermal hyperalgesia induced by carageenan injection into the footpad and reversed thermal hyperalgesia caused by constriction injury of sciatic nerve.

The results of the current study are consistent with the interpretation that the degree of sciatic motor and sensory blockade measured behaviorally depends not solely on the degree of impulse blockade in the sciatic axons, but also on the excitability of other locations in the nervous system, including the dorsal horn and perhaps also peripheral nociceptors. It is plausible that the basis for these effects lies in changes in excitability of dorsal horn neurons receiving synaptic inputs from primary sensory neurons. Further studies are in progress to examine this and alternative interpretations. It will also be of interest whether tachyphylaxis can be accelerated and prevented in other hyperalgesia models, such as the formalin model.

There may be a potential clinical role for use of NMDA antagonists to prevent or diminish tachyphylaxis, either in circumstances where prolonged blockade is required such as cancer, reflex sympathetic dystrophy or in settings where marked degrees of hyperalgesia are present as with reflex sympathetic dystrophy and other forms of neuropathic pain.

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