Neurologic Evaluation of the Rat during Sciatic Nerve Block with Lidocaine

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Background: Quantitative behavioral testing is necessary to establish a reproducible measure of differential functional blockade during regional anesthesia. Methods for assessment of the neurologic status (mental status, posture, gait, proprioception, motor function, autonomic function, and nociception) in veterinary neurology were adapted for the rat and used to monitor functional changes separately during a sciatic nerve block.

Methods: Sprague-Dawley rats were acclimated to laboratory routine before the study so that lidocaine (0.1 ml, 1%) could be injected near the sciatic notch without any chemical restraint. The onset, duration, and magnitude of functional losses were monitored. Proprioceptive integrity was evaluated by assessing the response to tactile placing and the hopping response. Extensor postural thrust, a test for postural reactions in small animals, was assessed on a digital balance and found adequate for quantifying motor function. Analgesia was assessed by measuring withdrawal response latencies to noxious thermal stimulation (51°C) and to superficial and deep noxious pinches. Autonomic function was monitored by measuring skin temperature. Contralateral limb function was used as an internal control, and injection of saline was used as an external control in separate, control animals.

Results: Onset of postural and gait abnormalities were observed as early as 40 s after injection. On each occasion proprioceptive impairment was detected first, followed by impairment of motor function and nociception. Complete absence of proprioception occurred from 10 to 30 min (n = 9) and of motor function at 30 min after injection (n = 10); both functions were fully recovered by 120 min. A unilateral increase in skin temperature on the foot was detected by 1 min; had reached its maximum change, 5.3 ± 0.7°C, at 10 min; and had returned to control levels at 60 min after injection (n = 12). Withdrawal response to cutaneous or superficial pain was absent in all ten animals from 5 to 30 min whereas the response to deep pain was absent in all ten animals at 20 min only. The response to noxious stimulation recovered at 90 min. Attention was paid to the temporal relation of the impairment of various functions.

Conclusions: Quantitative observations of the onset, offset, and intensity of differential functional impairment or block over time will make it possible to establish the doses and conditions for local anesthetics that result in differential nerve block and will permit comparison of these changes among different drugs and “clinical” protocols. (Key words: Anesthetics, local; lidocaine. Anesthetic techniques, sciatic nerve block: neurologic evaluation. Animals: rat.)

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at concentrations of LAs required to block impulses in different axons. In fact, a preliminary survey of myelinated and unmyelinated cutaneous afferent nerve fibers in the rat in vitro reveals a narrow range of lidocaine concentrations (0.2–0.6 mm) able to abolish all single impulses.

One factor that may resolve the discrepancy between observed functional and electrophysiologic assays, at least in part, is the length of nerve exposed to LA. Early work on cat saphenous nerve in vitro by Franz and Perry suggested that an absolute differential block by procaine between large-diameter, fast-conducting and small-diameter, slowly conducting fibers occurred only when the anesthetized nerve was less than 4 mm long. Intentional variation in exposure length in frog myelinated fibers reveals clearly the importance of exposure length for the critical blocking concentration of lidocaine. Hypotheses propose that the appearance of differential functional block during spinal and epidural procedures depends on the different length of spinal roots exposed to drug-containing medium in thoracic and spinal regions. However, to fit any data on impulse alteration to functional blockade a model to quantify functional changes reproducibly is necessary. To develop such a model was the purpose of this study.

To our knowledge, no publication has reported the effects of LAs on single afferent nerve fibers or even compound action potentials in vitro to correlate these findings with functional loss in a peripheral nerve block within a single animal species. In humans, although verbal communication makes it possible to measure functional loss independently, ethical issues prevent the high-resolution electrophysiologic evaluation of numerous compounds that are known to block nerve conduction in both in vitro and in vivo experiments. Thus there is a need to evaluate the effect of these compounds on the functions in animals from which neuronal tissue is used in neurophysiologic studies. In animals, however, the functional loss during peripheral nerve blocks is commonly evaluated by motor responses to noxious stimuli, and only gross discrimination between block of sensory and motor function has been attempted.

The goal of this study was to design a method permitting multifunctional neurologic evaluation in the rat, an animal widely used in neurophysiologic studies and with well-described behavior. We made the attempt to evaluate better the neuronal functions subserved by a nerve exposed to LA. We did not intend to describe the blocking efficacy of lidocaine but rather used this well-studied LA to establish the feasibility of a more detailed functional evaluation during peripheral nerve block. Using methods based on neurologic examinations in small animals, we quantitatively evaluated neuronal functions of the rat’s hind limb altered transiently by LA.

The evaluation considers sensory, motor, and sympathetic function in the limb under study. Although these functions are measured separately, because of their interactions their deficits can be interpreted only in the context of a complete functional evaluation. Better understanding of functional interrelations and their changes during a nerve block will facilitate the design of procedures to ablate one function selectively without impeding others—that is, the design of a truly differential nerve block. Preliminary results have been published.

Materials and Methods

Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 54–76 g were purchased at the age of 4 weeks and were handled daily during the next 20 days, at which time they had grown to an average body weight of 260 g. Except for 2 h (11:00 AM–1:00 PM), during which behavioral observations were done in the laboratory, animals were kept in separate cages in rooms with the rats of other investigators in the animal housing facilities of Brigham and Women’s Hospital, with controlled humidity, room temperature, and a 12-h (6:00 AM–6:00 PM) light–dark cycle. Animal treatment for all studies reported here was approved by the Harvard Medical Area Committee on Animals.

Handling

The goal of handling was to familiarize the animal with the experimenter, the environment in which the studies were done, the procedures involved in the neurologic evaluation and the injection procedure. Body weight was monitored daily. At the beginning of each training session each animal was placed alone in a Plexiglas (General Medical Engineering Corp., Peabody, MA) box, 45 × 35 × 20 cm high, for 3 min for observation of free behavior. The animal was observed for exploratory activity, and the latency of grooming, numbers of rearing, and of fecal boluses produced were monitored. This procedure allowed the animal to become familiar with the environmental conditions in the labora-
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R. Wilmington, Jr.

Animals were used at the age of 4 to 5 wk, and the next 20 wk. The average body weight was 150 to 200 g. The rats were injected with lidocaine (1% to 1.5% in saline) into the sciatic nerve of the hind limb. The sciatic nerve was exposed via a midline incision in the thigh. The nerve was located and the injection was made. The rats were placed in a holding cage and observed for signs of distress or discomfort. After the injection, the rats were returned to their home cage and observed for 24 h. The rats were then killed with an overdose of sodium pentobarbital and examined for signs of nerve damage.

Motor Function. Motor function was evaluated by observing the extensor postural thrust and by testing myotatic reflexes. The extensor postural thrust was quantified while the myotatic reflexes were observed for their presence or absence.

Extensor Postural Thrust. The rat was held upright with the hind limb extended so that the body's weight was supported by the distal metatarsal and toes, and the extensor thrust could be measured as the force applied to the digital platform balance (Ohaus LoPro, Fisher Scientific, Florham Park, NJ). The force that resists contact of the platform with the heel. Normal motor function was established by measuring the applied force necessary to bring the heel to the platform before LA injection (assigned 100% motor block score). The reduction in this force, representing reduced extensor muscle tone, was considered a deficit of motor function and expressed as a percentage of the control force. We recorded the normal force necessary to overcome any resistance to passive flexion of the hock without muscle tone and used this as a baseline to correct the measured active thrust. This passive force was measured in animals after the transection of the sciatic nerve at the incisura sacralis, with a 100% block of function.

Myotatic Reflexes. Myotatic reflexes were elicited by tapping the appropriate tendon or muscle belly with the handle of a pediatric plexor. The patellar reflex and the tibialis anterior reflex were chosen to compare the function of the nerve that has been exposed to the LA. Here the sciatic nerve, with the function of a nerve that has not been exposed to any drug. The patellar reflex is a monosynaptic stretch reflex of the extensor quadriceps femoris extensor muscle innervated by the posterior division of the femoral nerve, and the tibialis anterior reflex is a monosynaptic stretch reflex of the tibialis anterior muscle innervated by the deep peroneal branch of the sciatic nerve. Because of the enormous variations of the reflexes under control conditions, latency and amplitude of these reflexes were not graded but evaluated for presence and absence only. Both sensory and motor function had to be sufficiently intact for a given reflex to be elicited. Absence of reflexes in the continued presence of sensory and motor functions.

Neurologic Status. Mental status, posture, and gait were monitored throughout the observation period. This was done to test for the presence of stress, to monitor baseline behavior of the individual rat, to monitor the influence of a regional block on behavior, and to monitor possible systemic side effects from LA. Mental status was considered normal when the animal exhibited exploratory activity and was responsive to its environment. These behavioral aspects could be altered by systemic LA and are important to monitor because systemic effects could contaminate the evaluation of sensory, motor, and autonomic function in the limb under study. Asymmetries in gait and posture were first recorded by qualitative description, and the posture and gait abnormalities were quantified by specific tests for proprioception and motor function (see below).

Proprioception. Proprioception was evaluated by testing postural reactions. The functional deficit was graded as 0 (normal), 1 (slightly impaired), 2 (severely impaired), or 3 (absent).

Tactile Placing Response. While the rat was kept in a normal resting posture, toes of one foot were flexed with their dorsi placed onto the supporting surface, and the ability to reposition the toes was evaluated.

Hopping Response. The rat was placed with the hind legs on a supporting surface and the front half of the animal lifted off the ground (held upright by the evaluator). One hind leg at a time was lifted off the ground, and the animal's body was moved laterally. As soon as this happens an animal normally hops with the weight-bearing limb in the direction of movement to avoid falling over. With primarily proprioceptive disturbances the hopping response is delayed, and the magnitude of passive lateral movement must be greater to elicit a response; with primarily motor impairment there is a prompt response after initiation of a lateral movement, but the response is weaker than normal and the follow-through of the movement is impaired.
a false-negative result, must result from factors other than the block of the innervating nerve.

**Nociception.** Nociception was evaluated by observing the withdrawal of the limb in response to noxious stimulation.

**Withdrawal Reflex.** The withdrawal reflex (WR), also called the flexion reflex, was one of the reflexes used by Sherrington to illustrate many of the principles of reflex action. The WR of the hind limb involves contraction of flexor muscles in the hip, stifle (knee), and hock (ankle). It is a polysynaptic reflex that is induced by noxious stimulation of the limb and is latency, amplitude, and duration depend on stimulus intensity. We induced the WR by acute noxious stimulation of the skin (mechanical or thermal) or deep tissue (mechanical) at an intensity and repetition rate that did not result in hyperalgesia (table 1).

**Heat Stimulation (Cutaneous Pain).** Skin of the dorsum (hairy) or plantum (glabrous) of the foot was stimulated with a hand-held cylindrical metal probe with a tip diameter of 3 mm and the probe temperature maintained at 51.0 ± 0.5°C by circulating hot water. The probe was applied to the median margin of the metatarsus (primarily innervated by the saphenous branch of the femoral nerve) or the lateral metatarsus (primarily innervated by the tibial branch of the sciatic nerve) (figs. 1A and 1B). The presence or absence of flexion in the different joints was monitored, and the response latency was measured. The duration of stimulation necessary to induce a WR was measured in seconds and referred to as the time required for heat stimulation to elicit a WR.

**Mechanical Pinch Pain.** Forceps pinched the skin 2 mm wide over the lateral metatarsal pad and the distal phalanx (fig. 1C). On the forelimb, the skin between the tendons of the stimulation sites were rinsed with physiological saline in Cleveland, Ohio, and were kept cool with the stimulator.

**Autonomic Reflex.** Skin temperature was monitored by a thermistor attached to the skin that resulted in an increase in skin temperature reflecting peripheral neurovascular function.

**Skin Temperature.** Skin temperature was measured with a thermistor probe. Skin temperature was monitored before and during the stimulation of the nerve proximal to the point of stimulation.

**General Observations.** The animal was anesthetized with a general anesthetic, and the procedure was performed under sterile conditions.

**Pain Thresholds.** Pain thresholds were determined with a heat probe, a mechanical pinch device, and a noxious mechanical stimulus. The response latency for each stimulus was measured, and the time required for the WR to be elicited was recorded.

**Table 1. Observations on Control Side during Nerve Block**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin temperature (°C, n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Toe</td>
<td>27.1 ± 0.6</td>
<td>25.9 ± 0.3</td>
<td>23.9 ± 0.7</td>
<td>26.2 ± 1.4</td>
<td>26.9 ± 1.2</td>
<td>28.0 ± 0.8</td>
<td>26.2 ± 1.1</td>
<td>27.0 ± 1.2</td>
<td>26.9 ± 0.8</td>
</tr>
<tr>
<td>Heel</td>
<td>28.9 ± 0.6</td>
<td>26.7 ± 0.8</td>
<td>27.2 ± 1.2</td>
<td>28.3 ± 0.8</td>
<td>29.6 ± 0.7</td>
<td>30.1 ± 0.6</td>
<td>28.6 ± 0.8</td>
<td>29.3 ± 0.8</td>
<td>29.1 ± 0.7</td>
</tr>
<tr>
<td>Motor function (g, n = 15)</td>
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<tr>
<td>201 ± 22</td>
<td>208 ± 21</td>
<td>216 ± 22</td>
<td>216 ± 22</td>
<td>206 ± 21</td>
<td>215 ± 21</td>
<td>213 ± 21</td>
<td>220 ± 22</td>
<td>212 ± 21</td>
<td></td>
</tr>
<tr>
<td>Withdrawal response latency to heat (s, n = 14)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>DorLat</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.2 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.3 ± 0.1</td>
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<tr>
<td>DorMed</td>
<td>1.5 ± 0.1</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>PlaLat</td>
<td>2.1 ± 0.3</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>PlaMed</td>
<td>2.5 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Withdrawal response latency to pinch (s, n = 10)</td>
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</tr>
<tr>
<td>SkinLat</td>
<td>2.6 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>2.3 ± 0.2</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>DeepLat</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
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<tr>
<td>DeepMed</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*P < 0.05.

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sciatic nerve
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onds and termed “WR latency” (WRL). The cutoff time for heat stimulation was set at 10 s to avoid hyperalgesia.24

Mechanical Stimulation (Cutaneous and Deep Pain). Force calibrated forceps with a tip diameter of 2 mm were used to apply pressure across a skin fold over the lateral metatarsus (cutaneous pain) or across the distal phalanx of the first and fifth toe (deep pain) (fig. 1C). Care was taken to test, on the contralateral limb, the site of the foot closely mirroring the ipsilateral stimulation site. Intensity and duration of the stimulus were registered on a strip-chart recorder (Gould, Cleveland, OH) that was electrically coupled to the stimulating forceps.

Autonomic Function. Autonomic function was monitored by observing changes in skin temperature that result at least in part from changes in vasomotor tone reflecting sympathetic function of innervating peripheral nerves.25,26

Skin Temperature. The skin temperature (±0.1°C) was measured with a thermometer (871 Omega Digi- meter, Stamford, CT). The hand-held thermocouple was placed on the surface of the hairy skin at the heel and the base of the fifth toe on the ipsilateral and the contralateral foot until a stable reading was obtained.

General Protocol
The animals were observed as long as any sign of nerve block was detectable. Postural reactions, myotatic reflexes, and WRs were tested before and at 1, 5, 10, 20, 30, 45, 60, 75, 90, 105, and 120 min after the injection of LA. Rats were observed for abnormalities in gait and mental status throughout the block period.

Measuring all above mentioned parameters at a given time took less than 120 s. The measurements were always taken in the same order: (1) skin temperature, (2) proprioception (tactile placing response followed by hopping response), (3) motor function, and (4) nociception (heat follows 4 mm by cutaneous pinch and then by deep pinch). The order was chosen because we found in pilot experiments that this made it possible to minimize the effect of one test procedure on the succeeding test results.

Injection of Local Anesthetic
Our goal was to inject the LA without any chemical restraint, which would prevent evaluation of the early effects of the drug, or any major physical restraint, which may cause substantial stress and thus contaminate the neurologic examination. During the daily handling procedure animals were held in lateral recumbency, a very unusual position for rats, for increasing durations until they did not struggle in this position for 1 min. For injection the rat was held in lateral recumbency with the limb to be injected forming a right angle with the longitudinal axis of the trunk. The greater trochanter and ischial tuberosity were localized by palpation. On an imaginary line from the greater trochanter to the ischial tuberosity, about one third of the distance caudal to the greater trochanter, the injection needle was advanced from dorsolateral direction at a 45° angle until the tip encountered the ischium. Then 0.1 ml of 1.0% lidocaine hydrochloride (Xylocaine, Astra Pharmaceuticals, Westborough, MA), pH 6.4 ± 0.1, or isotonic saline was injected using a 27-G needle connected to a tuberculin syringe. This not only allowed for reliable delivery of the injectate in close proximity to the sciatic nerve but also for deposition of LA in comparable tissue compartments at different trials. In no instance was there any indication of trauma induced by the injection needle, either immediately after injection or in subsequent hours or days.

Data Collection and Analysis
Data for WRL and response latencies to noxious heat or pinch were recorded on an analog strip chart. The functions of the injected limb were compared with the functions of the noninjected limb. The observer was blinded to the treatment.

Onset and Offset of Functional Deficit. To estimate the sequence of functional impairment onset and their complete recovery, the frequencies and intensities of visible deficits immediately after LA injection and until complete recovery were compared.

Onset and Offset of Complete Loss of Function. The sequence of onset and offset of complete block of different functions were compared, and the significance of the differences between functions was estimated using a nonparametric Fisher test. Complete block to heat and mechanical stimulation could not be evaluated because of the stimulus intensity restriction. When the WRL to heat stimulation reached cutoff time, 10 s, the nociceptive function to heat was considered to be maximally blocked. Absence of WR to a pinch at 300 g was considered as complete block to mechanical stimulation.

Time Course of Functional Change. The magnitude of change in a given function (e.g., skin temper-
Table 2. Changes of Free Behavior during Handling Period

<table>
<thead>
<tr>
<th>Latency to grooming(s)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
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<tbody>
<tr>
<td>Day 1</td>
<td>35</td>
<td>68</td>
<td>74</td>
<td>38</td>
<td>43</td>
<td>45</td>
<td>47</td>
<td>30</td>
<td>49</td>
<td>68</td>
</tr>
<tr>
<td>Day 8</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Day 21</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>No. of fecal boli</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

Rat identifications are given as column heads.

nature) was compared with the magnitude of the measurement in the contralateral, nontreated leg.

**Statistics.** Statistical processing included two-tailed Student’s *t* test, Fisher’s exact probability test, and the chi-squared test. A probability value of 0.05 or less was considered significant. Microsoft Excel 4.0 (Redmond WA) was used for statistical calculations.

**Results**

**Free Behavior**

**First Observation.** When the rats were tested for the first time, initial behavior was recorded for 3 min before any handling was done. Rare ambulating, mainly along the wall of the box, was interrupted by postural freezing. The latency to the first grooming was 30–74 s, and the number of fecal boluses produced during an observation period (3 min) was three to nine (table 2).

**Observation on the 20th–30th Day of Handling.** Animals appeared calm without indications of stress, reflected in an adequate weight gain, complete absence of postural freezing throughout an observation period, and a continuous decrease in the number of boluses until none was found on days 10–15. The latency to the first grooming decreased during the first 5 or 6 days of handling (table 2).

**After Injection of Local Anesthetic or Saline.** Immediately after injection of LA or isotonic saline some of the rats became more active for about 1 min but without showing significant changes in the frequency of walking, rearing, sniffing, and grooming. Interestingly, they did not pay any special attention to the injected limb, during or after the nerve block. Furthermore, we did not observe any changes in free behavior throughout the observation period of 120 min when nothing was injected or when saline was injected.

**Nerve Block**

Repeated application of thermal or mechanical stimulation at time intervals to test for functional integrity of nociception did not reveal any statistically significant time-dependent trend or consistent differences on the contralateral limb in 14 animals after lidocaine injection (table 1) or on the ipsilateral limb after injection of isotonic saline. Thus, neither "learning" nor hyperalgesia or hyperesthesia occurred during the testing period.

**Qualitative Description of Observations during Nerve Block**

**Mental Status.** The animals were alert and responsive to the environment throughout the period of the nerve block.

**Skin Color.** Within the 1st min of the injection noticeable rubor of the glabrous skin in the foot developed and was present as long as the skin temperature was significantly greater than control levels.

**Posture.** Forty to 60 s after injection of LA the foot became slightly everted with more weight bearing on the lateral margin of the foot. The toes were less spread, were fully extended and were touching the supporting surface over their entire length, in contrast to plantar flexion in normal resting posture, and were pointing inward (medially). By 3 min after injection the toes were knuckled over ("clumping") on occasion, especially after locomotion. The hock was dropped, and the stifle, which is in a flexed position at resting posture.

**SCIATIC NERVE BLOCK**

under control conditions. There was no significant difference after injection of LA compared to saline last.

**Gait.** A marked weight-bearing shift occurred after 40 s, then again on knuckling of the toes after the injection of saline on the stifle; and lastly, 5–8 min after saline about 5 min. Interference of coordination appeared as weakness observed when walking.

**Myotatic Reflex.** It was difficult to elicit a myotatic reflex to the given stimulus in control and proponepidermized nerve. Thus, in no instance was a myotatic reflex and proprioceptive discharge observed on any occasion the test was performed and motor nerve was not selectively localized in the nervous system.

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**Myotatic Reflex.** It was difficult to elicit a myotatic reflex to the given stimulus in control and proponepidermized nerve. Thus, in no instance was a myotatic reflex and proprioceptive discharge observed on any occasion the test was performed and motor nerve was not selectively localized in the nervous system.

**Quantitative Description of Observations during Nerve Block**

**Mental Status.** The animals were alert and responsive to the environment throughout the period of the nerve block.

**Skin Color.** Within the 1st min of the injection noticeable rubor of the glabrous skin in the foot developed and was present as long as the skin temperature was significantly greater than control levels.

**Posture.** Forty to 60 s after injection of LA the foot became slightly everted with more weight bearing on the lateral margin of the foot. The toes were less spread, were fully extended and were touching the supporting surface over their entire length, in contrast to plantar flexion in normal resting posture, and were pointing inward (medially). By 3 min after injection the toes were knuckled over (“clumping”) on occasion, especially after locomotion. The hock was dropped, and the stifle, which is in a flexed position at resting posture.

**SCIATIC NERVE BLOCK**

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under control condition, was somewhat extended. There was a complete recovery of posture 105 min after injection with the posture of the toes recovering last.

**Gait.** A hardly noticeable ataxia and paresis with more weight-bearing on the lateral margin of the foot started after 40 s and progressed to intermittent weight bearing on knuckled toes at 3 min after injection. Dragging of the injected leg with movement in the hip, extended stifle, and weight-bearing on the knuckled paw started about 5 min after injection and lasted as long as 75 min. Interestingly, the rats did not show much reluctance for locomotion during motor impairment. It appeared as if this dysfunction did not bother them at all when walking on the bench-top.

**Myotatic Reflexes.** As mentioned in Methods, it is difficult to quantify the myotatic reflexes in the rat in the given conditions, and thus we could not always elicit an anterior tibial reflex although substantial motor and proprioceptive functions were present. However, in no instance could we elicit this reflex when motor and proprioceptive block were complete. On 12 occasions the patellar reflex could be readily induced at times when no anterior tibial reflex could be elicited, and motor function and proprioception of the sciatic nerve were completely blocked. This indicates the selective loss of a myotatic reflex consistent with the innervation of muscles in the hind limb.

**Quantitative Description of Observations during Nerve Block.**

Injection of LA did not result in any changes on the contralateral extremity, except that the temperature at the toe was slightly but significantly (P < 0.05) decreased 5 min after injection (table 1). Based on mean values for the times of onset, the order of impairment was as follows: tactile placing, hopping, and motor function, followed by skin temperature and nociception. In every animal (n = 12) posture was affected before nociception, and this impairment outlasted that of nociception.

**Skin Temperature.** One minute after injection the temperature of the skin at the toe was increased by 1.0 ± 0.04°C (mean ± SE; P < 0.01). Skin temperature reached a maximum at 10 min after injection (5.3 ± 0.7°C; P < 0.01), and had returned to baseline by 60 min. The temperature at the heel was increased by 1.8 ± 0.5°C (P < 0.01) by 1 min, reached its maximum at 20 min (3.9 ± 0.7°C; P < 0.01), and returned to control temperature by 60 min after injection (fig. 2).

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Fig. 2. Change in skin temperature at the toe and heel during block with local anesthetic. The values (mean ± SE; n = 12) represent the difference between skin temperature of treated and contralateral leg. *P < 0.05, **P < 0.01.

**Proprioception and Motor Function.** At the first measurement, 1 min after injection, proprioception tested by postural reactions was impaired in all nine animals tested (fig. 3A). Tactile placing response score changed by 2.0 ± 0.2 (mean ± SE; P < 0.01) and hopping response by 1.1 ± 0.2 (P < 0.01). Tactile placing response and hopping response were fully absent from 10 to 30 min and fully restored in all animals by 120 min after injection.

Motor function, expressed as the gram force of extensor postural thrust, was impaired in all ten animals tested at 1 min (fig. 3B). At that time it was reduced to 85 ± 13 g (mean ± SE; P < 0.01), from the control levels of 209 ± 21 g (mean ± SE). Complete, albeit transient, motor block was observed in all animals by 30 min. The motor function had fully recovered to control levels in nine of ten animals at 120 min after injection.

The tactile placing response (fig. 3A) was completely blocked in all rats at a time (5 min) when none of the animals had a complete motor block (fig. 3B). This finding indicates that the early proprioceptive deficit measured by the tactile placing response was not the
result of motor impairment but rather a result of sensory block.

Nociception. The onset of reduced nociception occurred later and complete recovery of nociception appeared sooner ($P < 0.001$) than the respective impairments of proprioception and motor function (figs. 4 and 5). At the first measurement after injection, thermal nociception was impaired in 50% of the animals at the dorsolateral and plantolateral paw (figs. 6B and 6D). At the dorsomedial site, WRL to heat was altered only slightly under any of the conditions studied (fig. 4), showing that the potential to withdraw was always present. Nociception was fully recovered for all conditions by 90 min after the injection (fig. 6A–6D).

Superficial versus Deep Pain. During onset of block impairment of the response to superficial pinch was more pronounced ($P < 0.05$) than to deep pinch. The mean magnitude of the WRL increase to lateral cutaneous pinch compared with lateral deep pinch was greater during onset of the block, and the mean maximal WRL change was reached sooner, at 7.5 min compared with 22.5 min (fig. 5). Both superficial and deep pinch responses, however, recovered to baseline by 80 min (figs. 5, 6A, and 6C). The overall time course of WRL to noxious heat (fig. 4) was similar to the time course of the response to superficial pinch (fig. 5). WRL to superficial pinch (tested to 300 g) was fully blocked in all seven animals after 30 min and lasted 30 min after the injection. Deep pinch was reduced to 50% at 10 min after the injection (fig. 6C). There was no further change in the average WRL increase during superficial pinch within the same animal. The single animal shown in fig. 5 shows that recovery was independent of the nature of the noxious stimuli.

Medial Impairment of locomotion (as measured by flexion of the hind legs) was reduced by dorsomedial LA injection (fig. 5). Except for the WRL to deep pinch ($P = 0.01$ for DorMed vs. DorLat, $P = 0.01$ for PlaMed vs. PlaLat), no other differences were found between the dorsal and plantolateral groups (figs. 4 and 5). The assumption that the effects of LA block extend only to the level of the LA injection was supported by the results of the recovery studies.
Sciatic Nerve Block with Lidocaine in Rat

**Pinch Response During LA Nerve Block**

![Graph showing pinch response during LA nerve block](image)

**Fig. 5.** Time course of changes in withdrawal reflex latency (WRL) to pinch of a skin fold on lateral foot (Skin lat) and deep pinch at the first (Deep med) and fifth toe (Deep lat) during local anesthetic nerve block. Plotted values represent mean ± SE. *P < 0.05, **P < 0.01, (n = 12).

In all seven animals tested at 5 min. The complete block lasted 30 min, and WRL returned to control levels 90 min after injection (fig. 6A). In contrast, WR to deep pinch was fully abolished in all animals at 20 min only (fig. 6C). Although there was no significant difference in the average times of complete recovery, WR to superficial pinch returned before deep pinch in every animal. This highly significant (P < 0.001) difference shows that analgesic potency of an LA depends on the nature or intensity of the noxious stimulus.

**Medial versus Lateral Stimulation.** Block or impairment of flexion in the stifle and hock did not abolish the WR completely; the limb could still be withdrawn by flexion in the hip. We observed no significant changes in WR for heat applied dorsomedially or deep pinch applied medially after LA injection (figs. 4 and 5). Except for dorsomedial heat stimulation and medial deep pinch the increase in WRL was significant (P < 0.01) for all stimulation sites from 5 to 45 min and for dorsolateral heat stimulation also at 2.5 and 6.15 min (figs. 4 and 5). These findings were consistent with our assumption that the medial aspect of the foot is innervated by the saphenous nerve and that therefore sensory functional integrity should be intact. However, the WR to plantomedial heat stimulation was prolonged similarly to the changes in WRL to heat stimulation and pinch at plantolateral sites (figs. 4 and 5). Transection of the sciatic nerve at the sciatic notch, the site of LA injection, revealed that skin at the plantomedial stimulation site (fig. 1B) was innervated by branches of the sciatic and not the saphenous nerve.

**Heat Stimulation of Glabrous versus Hairy Skin.**

At 5 min the WR to stimulation of the hairy skin was impaired in all animals, whereas it took 10 min until the WR to stimulation of the glabrous skin was impaired in all animals. At 5 min the WR to dorsolateral heat stimulation was absent in nine of ten rats whereas WR to plantolateral heat stimulation was absent in only five of ten rats (figs. 6B and 6D).

**Body Weight.** The body weight increased monotonically from 65.4 ± 7.8 g (mean ± SE; n = 10) at 4 weeks of age. Before handling was started, 393.1 ± 22.5 g at 13 weeks of age, 3 weeks after the end of nerve block studies. There is no indication of a slowing of growth during the time of the studies indicating that the animals did not experience stress sufficient to reduce their growth rate.

**Discussion**

Humans have long been intrigued by the difficulty of interpreting perception in animals. Lack of speech makes it necessary to search for alternative clues in behavior that communicate perception. This leads to very diverse interpretations, which are strongly influenced by culture and do not always benefit animals. Several reports describe pain tests in animals used for studying the physiologic mechanisms of nociception or peripheral nerve blocks with LAs (for review, see Grant et al.29). The tests used in these studies vary widely. In the majority, an overt motor response is used to measure pain sensation or the sensory disturbance caused by drugs, and little or no attention is paid to impairment of motor function itself resulting from the drug under study. Ironically, in studies in which motor function evaluation was attempted separately from the nociceptive response, it was assessed by measuring the amount of force generated during a motor task, unilateral hind-paw grip, ignoring that adequate sensory information is necessary for proper performance of this rather difficult motor task.

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A Pinch Superficial

B Heat Plantolateral

C Pinch Deep

D Heat Dorsolateral

Fig. 6. Percentage of animals with partial and complete block of withdrawal reflex to superficial pinch (A), deep pinch (C), heat stimulation of glabrous skin (B), and heat stimulation of hairy skin (D), resulting from local anesthetic sciatic nerve block.

With the goal to separate sensory from motor function we have chosen to evaluate postural reactions. The extensor postural thrust was considered appropriate for measuring the magnitude of motor function. This is a simple motor task, which maintains an animal's posture when it is held upright with only the posterior limbs supporting the body. With this test together with a proprioceptive evaluation one can discriminate between motor and sensory impairment as cause for gait abnormalities.

In animal nerve block studies, the interrelation of neuronal functions has been ignored. Activation of large-diameter afferent nerve fibers, for example, alters perception of information preferentially carried in small-diameter sensory afferent nerve fibers. Blocking myelinated afferent nerve fibers also changes the quality of sensation as shown in humans and prevents a response to noxious heat stimulation in dorsal horn cells of the cat. Block of tonic segmental input from afferent cutaneous nerve fibers alters motor function, as measured by the H-reflex. To assume that blocking one quality of sensation or one neuronal function can be achieved by blocking conduction in only the neuronal structure known to carry or encode this function is naive at best.

Although sympathetic function has been widely implicated in functional disorders such as neuropathic pain, little attention has been paid to sensory or motor changes resulting from lack of sympathetic outflow during a nerve block in animal studies. In normal physiologic conditions sympathetic efferent activity plays an important role in other functions. In addition to control of vasomotor tone, sympathetic activity has an impact on muscle function and sensory information. It has been implicated in the feedback loop for the regulation of excitability of muscle spindles. Removal of the superior cervical ganglion leads to increased sensitivity in the cat, and to improve in humans. Reduced sympathetic tone has also been observed in animals with peripheral nerve block. Therefore, it is possible that sensory and motor function might be influenced by a peripheral sympathetic nerve block. Given this, one might speculate that parallel peripheral sympathetic and sensory function might be influenced by this block. The present study shows that a direct block of the sciatic nerve results in a reduction of the H-reflex, which might indicate a spinal sympathetic function that is not observed in other studies. This might be due to the different experimental conditions and the different sensory thresholds that are necessary for nociceptive and non-nociceptive stimuli. When nerve block is performed, the stimulus threshold for nociception is reduced, whereas the stimulus threshold for non-nociception is increased.

When nerve block is performed in a WR, the H-reflex amplitude could be reduced and the reflex threshold could be increased. However, any reduction in the H-reflex amplitude might be due to the anesthetic agent itself and not to the nerve block. This result is consistent with the findings of previous studies that have shown a reduction in the H-reflex amplitude with nerve blocks.


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Increased sensitivity of the facial skin and of the cornea in the cat, and stellate ganglion block with LA leads to improvement of tactile sensation in the arm in humans. Reciprocally, noxious and nonnoxious cutaneous sensory stimulation results in increased sympathetic outflow. 12-12

Therefore, to describe a nerve block by LAs completely, it is necessary to evaluate the neurologic status, including mental status and all functions of the limb under study, and not merely to assess a single function, because it is impossible to separate these functions from each other in animals where the sensorium cannot be explored separately, as in humans. To merely use one or the other motor task for understanding pain sensation in animals ignores these relations and is an oversimplification of nociceptive or avoidance behavior.

In the existing literature the measurement of flexor reflex is referred to as a measure of threshold for nociception. We, on the contrary, realize that we do not know whether an animal withdraws as soon as it perceives pain, and thus we do not claim to measure the threshold for nociception. The WR, however, is a reflex to prevent injury by minimizing exposure to a noxious stimulus. Thus we consider the withdrawal of a limb to reflect nocifension resulting from nociception and we consider the WR a measurement of the nocifensive threshold, which may differ from the threshold for nociception.

When noxious stimulation of tissue does not result in a WR, sensory function, motor function, or both could be blocked. To solve this dilemma we have chosen to apply LA to the sciatic nerve. This can fully abolish any response to stimulation of the lateral aspect of the foot, but only moderately alters the response to stimulation of the medial aspect of the foot, especially on hairy skin, which is innervated by the saphenous nerve. When no WR results from stimulation of the lateral aspect of the foot but a robust WR results from stimulation of the medial aspect with flexion of the stifle and hock, then differential sensory but incomplete or no motor block is present. It must be remembered that despite complete block of flexor muscles of the stifle and hock the rat is able to withdraw the limb by flexion in the hip. Thus complete absence of a WR to noxious stimulation in the lateral foot is an indication that there is a sensory block of the stimulated skin area. It is very important not only to test for the presence and absence of the WR but also to identify the joints that are flexed during the WR. There was block of the WR to stimulation of the glabrous skin and not the hairy skin at the medial metacarpus (fig. 4) because the area innervated by the saphenous nerve of the glabrous skin (on the plantum of the foot) is smaller than that of hairy skin (on the dorsum) and because the chosen stimulus site was within the region innervated by the sciatic nerve.

The use of the hot-plate test, hot water immersion test or other methods in which the entire plantar surface is stimulated is not well suited to study changes resulting from manipulations of the sciatic nerve. Under such conditions the foot should be stimulated in a more restricted fashion otherwise tissue innervated by the saphenous nerve is stimulated too. Furthermore, we do not know how the remaining sensory input from the foot is interpreted under conditions where the sciatic nerve is blocked.

The difference in our results discriminating cutaneous or superficial pain from deep pain is interesting, because in most of the pharmacologic studies of nociception a cutaneous stimulus, heat stimulation, is used to induce pain without considering that pain of deep-tissue structures is usually involved in traumatic or postsurgical pain. Although the change in WRL to cutaneous pinch did not differ significantly from the change in WRL to deep pinch, examination of the percentage of animals exhibiting complete block does reveal significant differences. Furthermore, the difference in onset and recovery becomes even more significant considering that in each animal superficial pain was impaired or blocked before and recovered partially or completely after deep pain.

The nerve block attained here can be compared with single bolus sciatic nerve block in humans. In the rat we inject 2.5-3.3 mg/kg body weight (depending on the age). A successful sciatic nerve block in humans can be achieved with an injection of as little as 10 ml 2% lidocaine, which yields 200 mg or 2.8 mg/kg, within the range we used in the rat. For an adequately persistent, perioperative sciatic nerve block in humans the suggested dose is 20-30 ml 2% lidocaine, which yields 400-600 mg or 5.7-8.6 mg/kg, approximately 2.2 times the dose used in the rat.

In this study we could show that a more precise neurologic evaluation than commonly used during experimental regional block in the rat is possible and that it can be done reliably when animals are properly handled. Although this method may seem too time consuming when compared with commonly used pain tests in rats (tail flick, hot plate), the information gained about functional integrity during a peripheral nerve
block is much greater. Because the animals need not be tranquilized or anesthetized during injection of LA, there is no recovery period; the onset of functional changes can be observed immediately and functional deficit can be followed fully in time without other (e.g., pharmacologic) effects changing.

A general description of one deficit is given by $D(t) = f(P, L)$, where $D$ = functional deficit, a function of $t = time$, $P$ = probability of impulse blockade at $L$, the concentration of LA in nerve, $R$, = relation between the impulse blockade in a fiber type and the observed function. In separate experiments it should be possible to measure functional deficits, anesthetic function in the nervous tissue, and the dose-dependent probability of impulse blockade and thereby to establish the comparative pharmacodynamic and pharmacokinetic properties of different LAs. This method not only would allow for a more complete evaluation of functional integrity during a nerve block with LA, as used here, but will be well suited for evaluation of other neurologic conditions, as in studies of neuropathic pain. We are confident that by using this method to evaluate neurologic functions in rat more thoroughly we will gain better insight into how these functions interrelate and thereby understand better the underlying mechanisms of regional anesthesia and neurologic disorders.

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References


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