LABORATORY REPORTS

Anesthesiology
1997; 86:957-65
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Lippincott-Raven Publishers

Neurologic Evaluation of Infant and Adult Rats before and after Sciatic Nerve Blockade

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Background: **Only limited data exist comparing differences in sensory function and responses to neural blockade in infant and adult rats. Therefore, the authors sought (1) to compare baseline thermal, proprioceptive, and postural responses in infant, adolescent, and adult rats; and (2) to compare the effects of sciatic nerve blockade on thermal, proprioceptive, and postural responses in infant, adolescent, and adult rats.**

Methods: **Infant, adolescent, and adult rats were evaluated for proprioceptive, thermal, and mechanical nociceptive and motor function before and after sciatic blockade using a detailed neurologic examination.**

Results: **Mechanical and thermal nociception were present in all rats, starting from age 1 day. The withdrawal reflex latency to pinch was rapid at all ages, whereas that reaction to thermal stimulus depended on both age and temperature. In contrast, the tactile placing response and hopping response were absent at birth and developed completely during the first 10 days of life. The extensor postural thrust was absent in the first 2 weeks of life and developed variably during the first 50 days of life. Sciatic blockade duration is shorter in infant rats than in adult rats receiving the same dose per kilogram. A brief halothane general anesthetic at the time of sciatic injection in infant or adult rats does not alter the duration of blockade.**

Conclusions: **Infant rats show increased sensitivity to noxious thermal stimuli and similar response to deep mechanical stimuli compared with adult rats. Their proprioceptive and motor responses develop during the first 2 weeks of life. When doses are scaled by body weight, block duration is shorter in infant than in adult rats. (Key words: Rat, infant. Anesthetics, local: bupivacaine. Sciatic nerve. Nerve blockade.)**

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Received from the Department of Anesthesia, Children's Hospital, and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts. Submitted for publication August 20, 1993. Accepted for publication December 12, 1996. Supported by NIGMS 15904, the CHMC Anesthesia Foundation, and the Mayday Fund (to Dr. Berde) and the American Heart Association (to Dr. Delphine Hu).

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REGIONAL anesthesia has been used increasingly for infants and children in the past 10-15 yr, both as a sole anesthetic[1] and as a method for providing postoperative analgesia in patients receiving light general anesthesia.[2,3] Although regional anesthesia appears useful for infants and children, there are unresolved questions related to pain assessment and measurement and the pharmacokinetic and pharmacodynamic differences between infants and children.

The infant rat emerged as a useful model of peripheral and spinal nervous development and nociception primarily through the work of Fitzgerald and coworkers.[4-6] Their studies have shown that pain pathways and primitive nocifensive reflexes are present in infant rats from the time of birth. They have also shown that there is a rough parallelism in the development of peripheral nociceptive pathways and spinal connections among rats postnatal ages 1-14 days and those of human preterm and full-term infants from postconceptual ages 26-40 weeks.[5,7,8]

Thalhammer and coworkers[9] recently described an approach to neurologic examination in adult rats receiving sciatic nerve blockade. They emphasize quantitation of motor and proprioceptive functions in addition to nociceptive testing in nonstressed rats that have been habituated to a testing situation and are examined in natural spontaneous and reflex movements.

There are only limited data comparing sensory differences and responses to neural blockade in infant *versus* adult rats. Therefore we applied and modified the neurologic evaluation of Thalhammer and coworkers to study development of thermal and mechanical nociceptive, motor, and proprioceptive functions in infant rats before and after percutaneous sciatic nerve blockade.

Specifically, we wanted to confirm or reject the following hypotheses:

1. There is no difference between infant and adult rats in their thermal nociceptive, mechanical nociceptive, and proprioceptive responses.

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2. There is no difference between infant and adult rats in the duration of sciatic nerve blockade.
3. There is no difference between infant and adult rats in the order of recovery of thermal nociceptive, mechanical nociceptive, and proprioceptive responses after sciatic nerve blockade.

Methods

Infant Sprague-Dawley rats ages 1, 5, 9, and 12 days were raised as litters from dames purchased from Charles River Laboratories, (Wilmington, MA). Pregnant rats were monitored for newborn pups at 5 PM daily and pups born that day were considered to be age 0 days. Infant Sprague-Dawley rats ages 15, 20, 27, 35, and 70 days were purchased from Charles River Laboratories as a litter of dames and 14-day-old pups and raised until the desired age for experimentation. When the pups were 21 days old, they were separated from the dame and housed in small groups of four or five rats.

Except for the hours when behavioral observations were made in the laboratory, the rats were kept in the animal housing facilities of Children's Hospital, with controlled humidity, room temperature, and a 12-h light–dark cycle. Animal treatment for all studies was approved by the Children's Hospital Animal Care Committee.

Baseline Observations of Sensory and Motor Function in the Infant and Adult Rat

Sensory and motor function were evaluated in infant and adult rats before nerve blockade to establish the baseline neurologic function of rats at each age.

Proprioception. Proprioception was evaluated by testing postural reactions as described.[9]

Tactile Placing Response. With the rat supported upright in the examiner's hand, the toes of one foot were flexed with their dorsi placed onto the supporting surface and the ability to reposition the toes was evaluated. Special care was taken to keep the movement in the knee and the tibiotarsal joint to a minimum to avoid detecting altered position *via* femoral nerve afferents.

Hopping Response. The rat was placed with the hind legs on a supporting surface and the front half was lifted off the ground (held upright by the examiner). One hind leg at a time was lifted off the ground and the animal's body was moved laterally. As soon as this happens in a neurologically mature or unimpaired animal, it normally hops with the weight-bearing limb in the direction of movement to avoid falling over.[9]

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

Thermal Nociception. Skin of the plantar surface of the foot was stimulated by gently placing the hindpaw of the rat on the heated surface of a hot plate (3D, Analgesy Meter, IITC; Life Scientific, Woodland Hills, CA). In this hot plate test, the rat was gently wrapped in a towel from the waist up to restrict vision and upper body motion. One hindpaw was gently placed on the hot plate and the withdrawal reflex latency (WRL) was measured using a stopwatch. The contralateral hindpaw rests on a wooden block at room temperature. In this method, there is preferential application of the lateral plantar surface of the foot, so that there is minimal stimulation of saphenous nerve afferents.

It is important to note that our hot plate method differs from the traditional hot plate test, in which an animal is permitted to walk on all four extremities on the hot plate, and latency to limb shaking or paw licking is recorded.[10,11] The traditional method is useful for measuring systemic analgesic responses but is not useful for measuring blockade of a single extremity. In our method, first withdrawal of the limb from the hot plate is recorded. When used to assess sciatic blockade, rapid withdrawal on testing of the contralateral (unblocked) limb serves as a control for systemic analgesic or sedative actions of the local anesthetic.

Baseline withdrawal latencies to five different hot plate temperatures were obtained at 42°C, 46°C, 49°C, 52°C, and 56°C.

Mechanical Nociception. Forceps with a tip diameter of 2 mm were used to apply pressure across the distal phalanx of the fifth toe to elicit a withdrawal response.

Motor Function. Motor function was evaluated by measuring the extensor postural thrust.

Extensor Postural Thrust. The rat was held upright with the hind limb extended so that the body's weight was supported by the distal metatarsus and toes, and the extensor thrust could be measured as the force applied to the digital platform balance (Ohaus LoPro; Fisher Scientific, Floral Park, NJ), the force that resists contact of the platform by the heel. Baseline motor function was established by measuring the applied force necessary to bring the heel to the platform, and degrees of motor block were quantified by measuring the reduc-

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tion in weight in grams associated with heel contact after blockade. This method has been shown to be sensitive to degrees of blockade in our previous study of tachyphylaxis in adult rats.[11]

Sciatic Nerve Block by Injecting Local Anesthetic in the Infant and Adult Rat

A posterior approach was used for sciatic nerve injection. At a point halfway between the greater trochanter and the stifle (knee) and just posterior to the femur, the injection needle was advanced (typically 3–7 mm, depending on the size of the animal) and the local anesthetic was injected. For rats 35 days old or younger, a 30-gauge needle was connected to a 1-ml syringe. For adult rats, a 26-gauge needle was connected to a 3-ml syringe. The contralateral limb was injected with a comparable volume of normal saline to serve as a control. For all studies reported, 0.5% bupivacaine (Sensorcaine; Astra Pharmaceuticals, Wesborough, MA) was injected in a dose of 5 μl/g for rats 5, 15, 35, and 70 days old. Five-day-old rats weighed approximately 10 g and received injection volumes of about 50 μl. Pilot studies of 1- and 3-day-old animals showed severe sedation and some deaths (20% in 1-day-old rats) with these large doses, so that data for 1- and 3-day-old animals were not included in the present study.

Proprioception and thermal and mechanical nociception were measured every 20 min until neurologic function returned to baseline.

To determine whether the measured duration of blockade of thermal nociception varied with the intensity of the heat stimulus, two hot plate temperatures were used—52°C and 56°C.

Effect of a Brief General Anesthetic on Block Duration

Previous pilot studies found that adult rats were susceptible to movement during injection and that they sometimes became combative and stressed when injected repeatedly. Thus control studies were performed to compare blockade durations in groups of infant, adolescent, and adult rats that were randomly assigned to receive blockade either awake or under a brief (60 s) halothane anesthetic (4% inspired concentration in oxygen *via* mask for 10–20 s, 1% thereafter).

Data Collection and Analysis

The tactile placing response (TPR), hopping response (HR), and withdrawal response to mechanical stimulation were graded as present or absent.

Table 1. Development of the (1) Hopping Response (HR), (2) Toe Pinch Response (TP), and (3) Toe Placing Response (TPR) in Rats Age 1–70 Days.*

	% of Animals with Response		
Rat Age (d)	HR	TP	TPR
1	0	100	0
5	0	100	0
9	100	100	63
12	100	100	100
15	100	100	100
21	100	100	100
27	100	100	100
70	100	100	100

* Values below represent the percentage (%) of animals with each response at a given age.

In the hot plate test, the withdrawal response latency was measured by stopwatch to a maximum cutoff time of 12 s at 56°C and 15 s at 52°C. After the cutoff time, if the rat's hindpaw still remained on the hot plate, the hindpaw was removed from it to prevent heat injury (*i.e.*, blistering). At each time point, the WRL was measured in triplicate and the mean of these three measurements was considered to be the WRL for that time point. When local anesthetic was injected, almost all rats reached the maximum WRL of 12 or 15 s, and the duration of nerve block was considered to be the time until the mean WRL decreased to less than 6 s at 56°C and 7.5 s at 52°C.

Statistical Analyses

Group comparisons were made for unpaired parametric data using analysis of variance with *post hoc* Student-Neuman-Keuls tests (between-group comparisons) and with either Kruskall-Wallis or chi squared tests for nonparametric data. For paired data, a repeated-measures analysis of variance was performed with Bonferroni corrected paired *t* tests for *post hoc* comparisons. A probability value less than 0.05 was considered significant.

Results

Baseline Sensory and Motor Function in Infant and Adult Rats

Tactile Placing Response. The TPR was absent in 100% of 1- and 5-day-old (table 1) rats. When the toes of one foot were flexed, none of the rats responded

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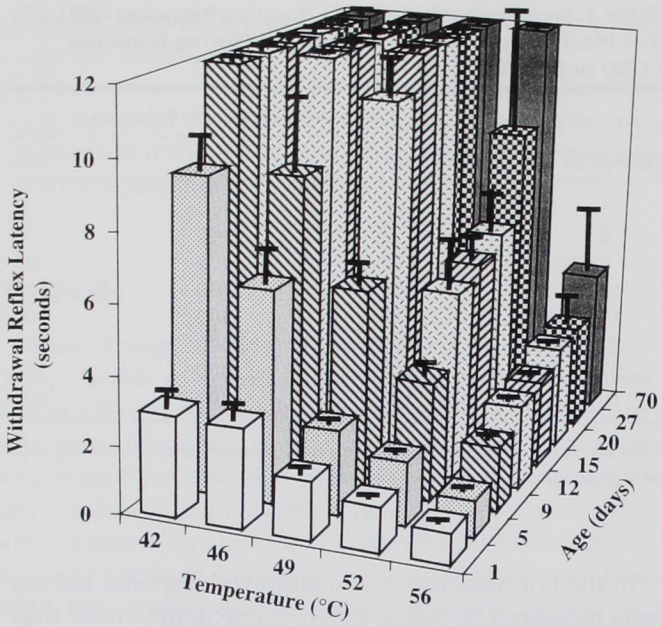

Fig. 1. Three-dimensional graph of changes in the withdrawal reflex latency to heat stimulation of the foot as (1) the hot plate temperature and (2) rat age are varied. Values plotted represent means ± SD. In 27- and 70-day-old rats, the withdrawal reflex latencies plotted at 52°C and 56°C represent values measured after 5 days of habituation. This figure represent baseline data for 1-, 5-, 9-, 12-, 15-, 20-, 27-, and 70-day-old rats in the absence of local anesthetic sciatic nerve blockade (n = 8).

by repositioning the toes, even after a 10-s period of observation. By 9 days of age, 63% of rats developed the TPR. However, compared with adults rats, this response was not yet mature and the response time was delayed ($P < 0.05$). By age 15 days, the TPR was equivalent to that observed in adult rats. In 15-day-old rats, as with adults, the TPR occurred briskly (<1 s) after toe flexion.

Hopping Response. The HR was completely absent in all 1- and 5-day-old rats (table 1). This test resulted in dragging of the foot with no attempts at hopping. By age 9 days, an HR could be elicited from all of the rats ($P < 0.05$ for each pairwise comparison of groups of rats age 9 days and older compared with the 1- and 5-day-old groups). Compared with adult rats, 9-day-old rats had an HR response that was impaired. The hopping was not as finely coordinated as with adults, and the HR could be stopped with repeated testing. In rats 21 days and older, the HR was identical to that observed in the adult. Table 1 describes the development of the hopping response in 1–70-day-old rats.

Mechanical Nociception. The withdrawal response to toe pinch was elicited in 100% of rats age 1 day and older (table 1). When pressure was applied with forceps to the fifth phalanx, an immediate withdrawal-response latency of less than 1 s occurred in rats of all ages. There were no differences in WRL with age ($P > 0.05$ for each paired comparison).

Thermal Nociception.

Effect of Age on the Withdrawal Reflex Latency. For every testing temperature, mean withdrawal reflex latencies (WRLs) increased with age (fig. 1). At the higher temperatures of 56°C and 52°C, adult rats had longer WRLs ($P < 0.01$) than did all infant rats. At the lower testing temperatures of 49°C to 42°C, the percentage of infant rats with the cutoff WRL of 12 s increased. At 42°C, rats 9 days and older generally reached the cutoff latency of 12 s, similar to adults. At all temperatures, 1- and 5-day-old rats had significantly

Table 2. Duration of Blockade of the (1) Hopping Response (HR), (2) Toe Placing Response (TPR), and the Withdrawal Reflex to (3) the Hotplate Test (HP) and (4) Toe Pinch (TP) Resulting from Sciatic Nerve Injection of Bupivacaine in Which Rats Were Tested on a Hotplate of Either 52° or 56°C.*

	Duration of Blockade (min)	
Rat Age (d)	HR 52°	HR 56°
5	**	**
15	150 ± 20	160 ± 30
35	163 ± 15	160 ± 26
70	295 ± 9	295 ± 9
	TPR 52°	TPR 56°
5	**	**
15	160 ± 26	158 ± 29
35	158 ± 29	160 ± 26
70	298 ± 15	295 ± 9
	HP 52°	HP 56°
5	163 ± 26	117 ± 20
15	175 ± 17	143 ± 26
35	210 ± 11	186 ± 10
70	393 ± 20	343 ± 17
	TP 52°	TP 56°
5	143 ± 17	137 ± 9
15	138 ± 15	130 ± 14
35	140 ± 20	145 ± 29
70	293 ± 12	290 ± 12

* Values below represent means ± standard deviation.

** In 5-day-old rats, the hopping response and toe placing response was not present and therefore was not measured.

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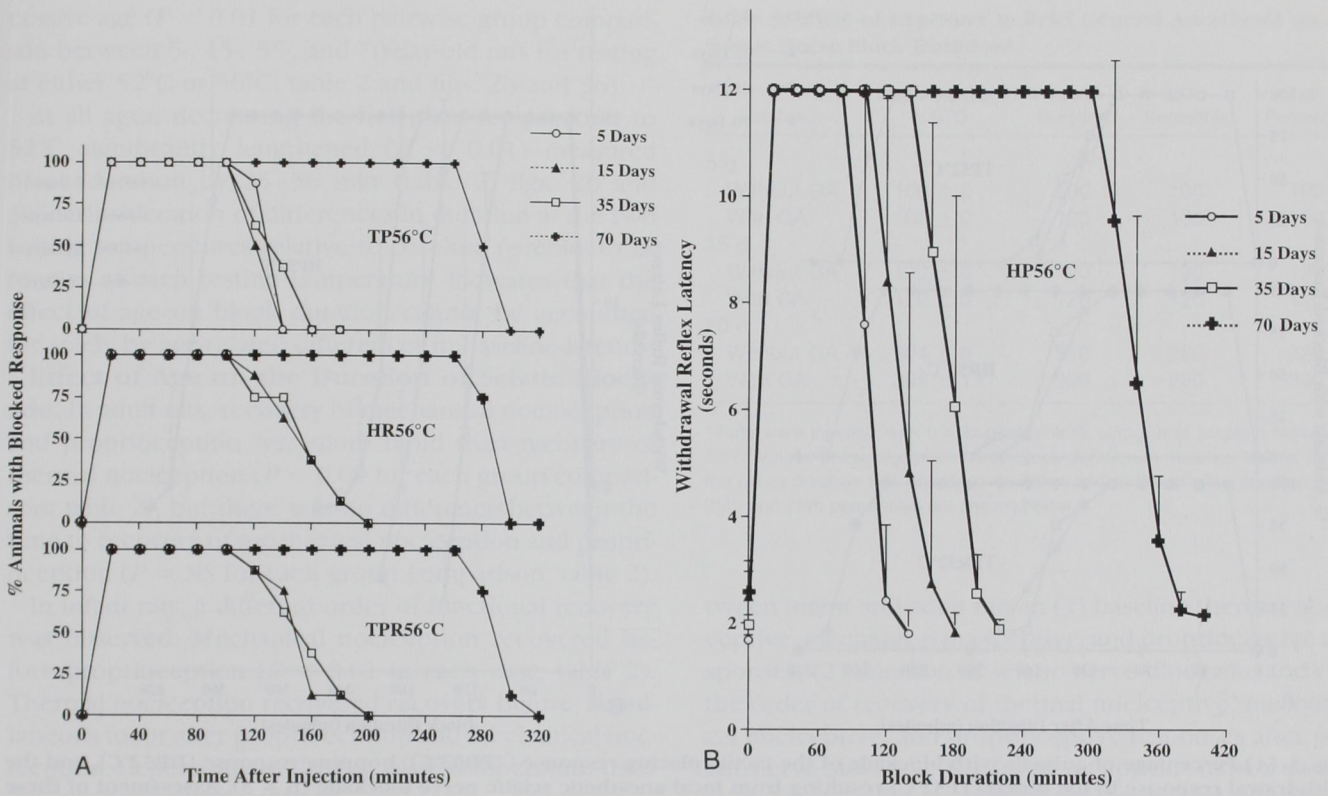

Fig. 2. (*A*) Percentage of animals with blockade of the tactile placing response (TPR56°C), hopping response (HR56°C), and the withdrawal response to toe pinch (TP56°C) resulting from local anesthetic sciatic nerve blockade (n = 8). Assessment of these functions followed measurement of the withdrawal reflex latency to a 56°C hot plate. In 5-day-old rats, the tactile placing and hopping responses were not present. (*B*) Time course of changes in the withdrawal reflex latency to noxious heat stimulation of 56°C (HP56°C) resulting after local anesthetic sciatic nerve blockade. Plotted values represent means ± SD. A cutoff time of 12 s was used when rats were tested on the hot plate at 56°C.

shorter WRLs than did all older rats ($P < 0.001$ for each group comparison).

Effect of Hot Plate Temperature on the Withdrawal Reflex Latency. For each age group, WRLs decreased with increasing testing temperatures (fig. 1). At 56°C, rats of all ages reacted briskly to the hot plate and their WRLs were 4.3 s or less (fig. 1). Compared with testing at 56°C, testing at 52°C produced longer WRLs and the untrained (*i.e.*, in rats that were not exposed to the hot plate previously) adult WRL increased to the cutoff value of 12 s. Lower testing temperatures produced further increases in WRLs and increased the percentage of infant rats exhibiting the cutoff WRL of 12 s. One-day-old rats reacted briskly to the hot plate at all temperatures, with WRLs of 3 s or less (fig. 1), even as the temperature was reduced to 42–44°C. One-day-old rats do not withdraw the contralateral foot from the wood block at room temperature, suggesting that their withdrawal from the hot plate even at 42–44°C may represent a nocifensive response and not simply a tactile reflex response to placing the foot on a surface.

Rats younger than 27 days old had relatively constant baseline thermal latencies on repeated testing on successive days. Repeated daily testing of 27-day-old and adult rats produced slight shortening of baseline latencies during a period of 3–5 days when test temperatures at 56°C and 52°C were used. For example, rats repeatedly tested during a period of 4 days at 56°C had a reduction in mean baseline latencies from 4 to 2.5 s.

Extensor Postural Thrust. The extensor postural thrust could not be measured accurately in 1-, 5-, 9-, or 12-day-old rats. When the hind limb was extended, the rat's heel was easily brought into contact with the surface of the scale with little or no resistance. In 15- and 21-day-old rats, the extensor postural thrust ranged from 33–51 g and 38–67 g, respectively, but these measure-

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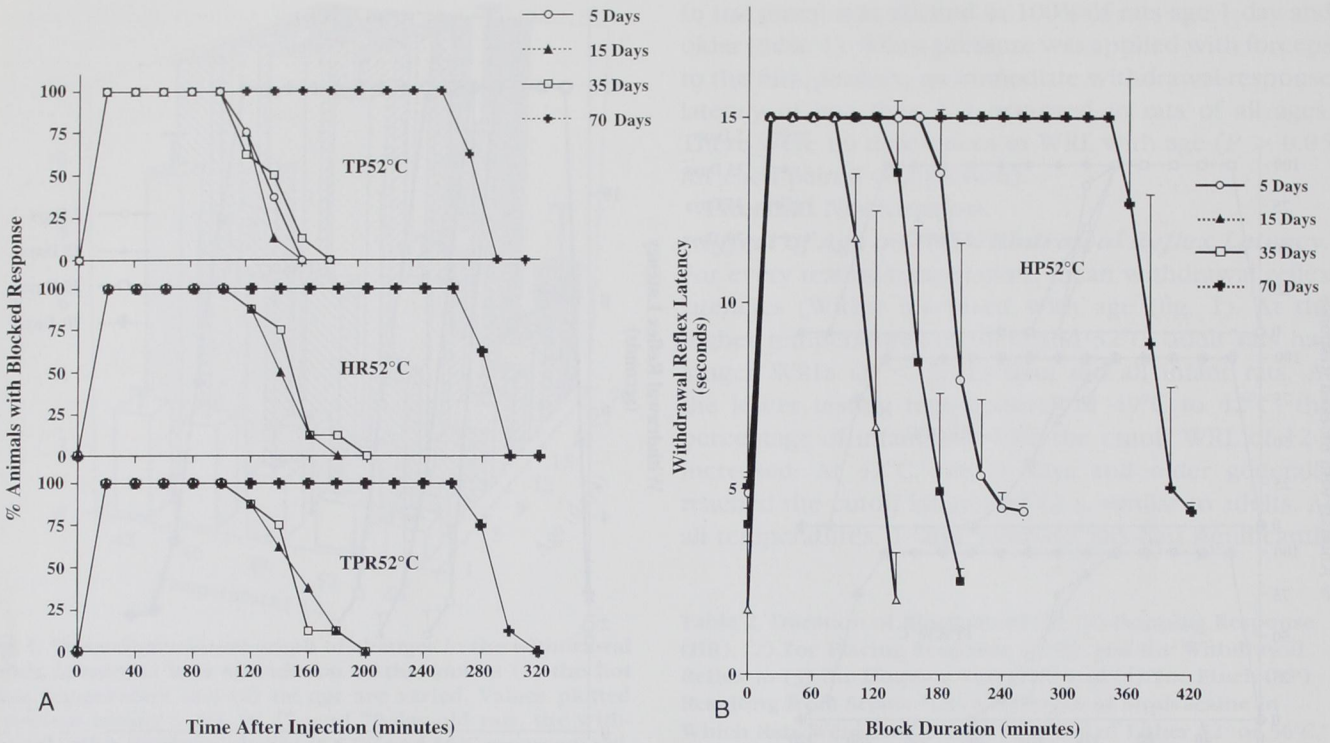

Fig. 3. (*A*) Percentage of animals with blockade of the tactile placing response (TPR52°C), hopping response (HR52°C), and the withdrawal response to toe pinch (TP52°C) resulting from local anesthetic sciatic nerve blockade (n = 8). Assessment of these functions followed measurement of the withdrawal response latency to a 52°C hot plate. In 5-day-old rats, the tactile placing and hopping responses were not present. (*B*) Time course of changes in the withdrawal reflex latency to noxious heat stimulation of 52°C (HP52°C) resulting after local anesthetic sciatic nerve blockade. Plotted values represent means ± SD. A cutoff time of 12 s was used when rats were tested on the hot plate at 56°C.

ments were inconsistent and varied greatly secondary to fatigue after two or three repeated measurements. Adult rats showed consistent extensor postural thrust measurements on repeated testing.

Responses to Sciatic Nerve Blockade

Sciatic nerve injection with 0.5% bupivacaine in a dose scaled to body weight (5 μl/g) produced complete blockade of nociception, proprioception, and motor function in all rats in all age groups within 20 min.

Duration of blockade of each function was longer in 27-day-old rats and adults than in all groups of infants ($P < 0.01$ for each group comparison; table 2).

Proprioception: Tactile Placing Response and Hopping Response. In 15- and 35-day-old rats, TPR and HR fully recovered between 150 and 163 min. Adult rats had a longer duration of proprioceptive loss ($P < 0.01$), with full return of TPR and HR by 300 min. Measurement of proprioceptive block was not possible in 5-day-old rats because the TPR and HR had not yet developed at that age. In groups of animals 9 days and older, the duration of proprioceptive block was not changed by simultaneous testing with hot plate temperatures of either 52°C or 56°C (table 2, figs. 2a and 3a).

Mechanical Nociception. In 5-, 15-, and 35-day-old rats, sciatic blockade with bupivacaine completely blocked the withdrawal response to toe pinch for 130 to 145 min. For 5-, 15-, and 35-day-old rats, response to pinch returned before proprioception ($P < 0.01$ for each comparison; table 2, figs. 2a and 3a).

In adult rats, a different pattern was observed. Recovery of mechanical nociception occurred simultaneously with recovery of proprioception ($P > 0.05$). Simultaneous thermal testing with hot plate temperatures of 56°C to 52°C did not change measured duration of blockade of mechanical nociception in any age group.

Thermal Nociception. The duration of blockade measured by hot plate testing increased with each suc-

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cessive age ($P < 0.01$ for each pairwise group comparison between 5-, 15-, 35-, and 70-day-old rats for testing at either 52°C or 56°C; table 2 and figs. 2b and 3b).

At all ages, decreasing the hot plate temperature to 52°C significantly lengthened ($P < 0.01$) measured block duration by 25–36 min (table 2, figs. 2b and 3b). Consideration of differences in duration at the two testing temperatures relative to baseline (preblock) latencies at each testing temperature indicates that the effect of age on block duration cannot be accounted for solely by age-related differences in baseline latency.

Effect of Age on the Duration of Sciatic Blockade. In adult rats, recovery of mechanical nocioception and proprioception was more rapid than recovery of thermal nociception ($P < 0.01$ for each group comparison; table 2), but there was no difference between the time to recovery of mechanical nociception and proprioception (P = NS for each group comparison; table 2).

In infant rats, a different order of functional recovery was observed: Mechanical nociception recovered before proprioception ($P < 0.01$ in each case; table 2). Thermal nociception recovered recovery before, simultaneous to, or after proprioception and mechanical nociception, depending on the hot plate temperature used for sensory testing (table 2).

Duration of blockade of mechanical nociception, motor function, and proprioception was unchanged by parallel hot plate testing of the animals at either 52°C or 56°C ($P > 0.05$ for each comparison). Table 2 summarizes mean block durations for each function.

Effect of a Brief General Anesthetic on Block Duration. For all age groups, a brief general anesthetic had no effect on the duration of sciatic blockade, as shown in table 3.

Toxicity. No loss of function was measured in the contralateral leg of any animal, which suggests that the effects measured are due to regional anesthesia of the sciatic nerve, rather than to systemic impairment of sensory, motor, or proprioceptive functions by high circulating concentrations of bupivacaine. Despite the large doses used, no seizures or other behavioral signs of systemic toxicity were observed in any animals 5 days and older. All animals fully recovered nociceptive, proprioceptive, and motor function after blocks; no signs of nerve injury were evident in any animal.

Table 3. Effect of Exposure to Brief General Anesthesia on Sciatic Nerve Block Duration*

Rat Age	Mean Duration ± STD	Median Duration	25th Percentile	75th Percentile
5 d				
Without GA	100 ± 0	100	100	100
With GA	100 ± 0	100	100	100
15 d				
Without GA	120 ± 0	120	120	120
With GA	120 ± 0	120	120	120
70 d				
Without GA	304 ± 9	310	280	320
With GA	308 ± 11	320	280	340

* Rats were injected with 5% bupivacaine (5 μl/mg) and hotplate tested at 56°C. Values below represent nerve block duration in minutes. Values for a) the mean duration with standard deviation and b) the median duration with 25th and 75th percentiles are shown below.

Discussion

The first three hypotheses tested in the study were rejected. Significant differences were observed between infant and adult rats in (1) baseline thermal nociceptive, mechanical nociceptive, and proprioceptive responses; (2) duration of sciatic nerve blockade; and (3) the order of recovery of thermal nociceptive, mechanical nociceptive, and proprioceptive responses after sciatic nerve blockade. The infant rat appears to be a useful model system for examining developmental effects on local anesthetic action. Several neurologic functions can be monitored and undergo developmental changes.

Thermal and mechanical nocifensive responses were brisk even in 1-day-old rats, whereas responses that depend on proprioception developed at varying rates during the first 2–3 weeks of life. This parallels development in the human infant, in which nociceptive responses develop rapidly, but proprioceptive and motor reflexes of the lower extremities develop more slowly during the first 2 yr of life. Immaturity of proprioceptive and motor reflex functions in the infant may be related in part to incomplete myelination of Aβ fibers[12] as well as to delayed maturation of tracts in the spinal cord.[13] Previous studies of rat and human infants by Fitzgerald and coworkers[6] outlined the ontogeny of threshold responses to von Frei hair testing. They found that newborn rats and humans have a lower threshold to von Frei hairs compared with older infants and that the threshold stimulus increases with increasing age. Similarly, Stelzner[14] found a lower threshold to electrical stimulation in newborn rats. Consistent with their results, we found a parallel increased sensitivity to thermal nociception in newborn rats compared with older rats. The increased sensitivity to nociception in new-

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born rats may be enhanced somewhat by delayed maturation of spinal descending pain-inhibitory systems.[13]

Previous work on maturation of responses to analgesics in infant rats have had somewhat mixed results. Pasternak *et al.*[15] found minimal analgesic activity of morphine in thermal or pressure analgesic tests before 7 days of age. In contrast, Abbott and Guy[16] recently reported that specific pain behaviors could be detected in the formalin model in rats as young as 1 day old, and that these behaviors were differentially sensitive to morphine compared with pentobarbital.

The differences in order of recovery after sciatic blockade were of interest. In infants, nociception recovered more slowly than did proprioception, whereas in adults the opposite was seen.

Previous studies of local anesthetic actions in infant animals primarily examined either topical application or systemic administration to assess toxicity. Badgwell and coworkers[17] developed a piglet model for age-related effects on local anesthetic systemic toxicity. We could not identify previously used infant whole-animal models assessing neurologic function in response to local anesthetic peripheral nerve blockade. Excised infant and adult rabbit vagus nerves *in vitro* were studied by Benzon and coworkers,[18] who found at most a slightly increased susceptibility to lidocaine blockade of infant rabbit nerves.

The shorter duration of blockade in infant animals compared with adult animals receiving the same dose and volume per kilogram is of interest. Few clinical data exist comparing duration of peripheral nerve blocks in infant and adult humans. Spinal anesthesia has a much shorter duration in infants compared with adults, even when larger doses per kilogram are given to infants,[1] but the factors influencing block duration may be different for spinal anesthesia compared with peripheral nerve blockade. Developing peripheral nerves have several anatomic and functional differences from adult peripheral nerves that may modify responses to local anesthetic blockade. These include differences in myelination, differences in the thickness and permeability of the epineurium, differences in nerve diameter, differences in sodium channel number and local density, and differences in the spacing and number of nodes of Ranvier.[19] However, exactly how these factors may affect local anesthetic action and duration is not known and requires further investigation.

In conclusion, we have developed a model for testing neurologic function in the developing rat both at baseline and after sciatic nerve blockade with bupivacaine. At baseline, infant rats have pain responses starting from the first day of life. Compared with adults, infant rats have increased sensitivity to noxious thermal stimuli but show a similar response to mechanical stimuli. Proprioceptive and motor responses develop during the first 2 weeks of life. With sciatic nerve blockade using doses of bupivacaine scaled to body weight, blockade duration is shorter in infant than in adult rats. These neurologic differences between infant and adult rats parallel neurologic differences found in humans. We hope that the model system described here will permit further exploration of factors that modify peripheral nerve function and local anesthetic block duration.

The authors thank Drs. Gary Strichartz and Johann Thalhammer for providing encouragement and helpful discussions.

References

1. Abajian J, Mellish R, Browne A, Perkins F, Lambert D, Mazuzan JJ: Spinal anesthesia for surgery in the high-risk infant. Anesth Analg 1984; 63:359–62

2. Meignier M, Souron R, Leneel J: Postoperative dorsal epidural analgesia in the child with respiratory disabilities. ANESTHESIOLOGY 1983; 59:473–5

3. Krane EJ, Jacobson LE, Lynn AM, Parrot C, Tyler DC: Caudal morphine for postoperative analgesia in children: A comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 1987; 66:647–53

4. Fitzgerald M, Swett J: The termination pattern of sciatic nerve afferents in the substantia gelatinosa of neonatal rats. Neurosci Lett 1983; 43:149–54

5. Fitzgerald M: The development of activity evoked by fine diameter cutaneous fibres in the spinal cord of the newborn rat. Neurosci Lett 1988; 86:161–6

6. Fitzgerald M, Shaw A, MacIntosh N: Postnatal development of the cutaneous flexor reflex: Comparative study of preterm infants and newborn rat pups. Dev Med Child Neurol 1988; 30:520–6

7. Fitzgerald M: Development of pain mechanisms (Review). Br Med Bull 1991; 47:667–75

8. Fitzgerald M, Millard C, McIntosh N: Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. Pain 1989; 39:31–6

9. Thalhammer JG, Vladimirova M, Bershadsky B, Strichartz GR: Neurologic evaluation of the rat during sciatic nerve block with lidocaine. ANESTHESIOLOGY 1995; 82:1013–25

10. Masters DB, Berde CB, Dutta SK, Griggs CT, Hu D, Kupsky W, Langer R: Prolonged regional nerve blockade by controlled release of local anesthetic from a biodegradable polymer matrix. ANESTHESIOLOGY 1993; 79:340–6

11. Lee KC, Wilder RT, Smith RL, Berde CB: Thermal hyperalgesia accelerates and MK-801 prevents the development of tachyphylaxis to rat sciatic nerve blockade. ANESTHESIOLOGY 1994; 81:1284–93

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12. Gilles FH, Shankle W, Dooling EC: Myelinated tracts: Growth patterns, The Developing Human Brain. Edited by Gilles FH, Leviton A, Dooling EC. Boston, Wright & Co., 1983, p 117

13. Fitzgerald M, Koltzenburg M: The functional development of descending inhibitory pathways in the dorsolateral funiculus of the newborn rat spinal cord. Dev Brain Res 1986; 24:261-70

14. Stelzner DJ: The normal postnatal development of synaptic end-feet in the lumbosacral spinal cord and of responses in the hind limbs of the albino rat. Exp Neurol 1971; 31:337-57

15. Pasternak GW, Zhang AZ, Tecott L: Developmental differences between high and low affinity opiate binding sites: Their relationship to analgesia and respiratory depression. Life Sci 1980; 27:1185-90

16. Abbott FV, Guy ER: Effects of morphine, pentobarbital and amphetamine on formalin-induced behaviors in infant rats: Sedation versus specific suppression of pain. Pain 1995; 62:303-12

17. Badgwell JM, Heavner JE, Kytta J: Bupivacaine toxicity in young pigs is age-dependent and is affected by volatile anesthetics. ANESTHESIOLOGY 1990; 73:297-303

18. Benzon HT, Strichartz GR, Gissen AJ, Shanks CA, Covino BG, Datta S: Developmental neurophysiology of mammalian peripheral nerves and age-related differential sensitivity to local anaesthetic. Br J Anaesth 1988; 61:754-60

19. Webster H: The geometry of peripheral myelin sheaths during their formation and growth in rat sciatic nerves. J Cell Biol 1971; 48:348-67

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