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Focal Conduction Block in the Dorsal Root Ganglion in Experimental Allergic Neuritis

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Abstract

Acute experimental allergic neuritis was induced in Lewis rats by inoculation with bovine intradural root myelin and adjuvants. In terminal experiments, sensory conduction was assessed in rats with hindlimb ataxia and weakness by stimulating the exposed sciatic nerve and recording directly from the exposed L-4 spinal nerve, dorsal root ganglion, dorsal root, and dorsal root entry zone. Focal conduction block was present in a high proportion of large-diameter fibers in the dorsal root ganglion. In contrast, nerve conduction in the peripheral nerve and spinal nerve was essentially normal apart from probable conduction block in some fibers in the proximal spinal nerve in a minority of rats. The afferent volley arriving at the dorsal root entry zone of the spinal cord was greatly reduced, as a consequence of the conduction block in the dorsal root ganglion and probable conduction block in the dorsal root. The M wave recorded from the fourth dorsal interosseus muscle of the hindfoot was normal in amplitude but slightly prolonged in latency and the H reflex was absent. These electrophysiological findings correlated well with the histological findings of inflammation and prominent demyelination in the dorsal root ganglia and dorsal roots with minimal involvement of the proximal spinal nerve and no involvement of the sciatic nerve. It is concluded that the hindlimb ataxia in rats with this form of acute experimental allergic neuritis is due to demyelination-induced nerve conduction block in the dorsal root ganglia and probably in the dorsal roots.

Experimental allergic neuritis (EAN) is an autoimmune demyelinating disease of the peripheral nervous system (PNS) induced by inoculation with PNS tissue [1] or P2 protein [2] and adjuvants. In its acute form, it is widely studied as an animal model of the human disorder, the Guillain-Barré syndrome. The distribution of lesions in the PNS differs among different models of acute EAN. In rabbits and mice with acute EAN induced by inoculation with whole PNS tissue, the dorsal root ganglion is the most consistently affected region of the PNS [1,3]. The dorsal root ganglion is also a major site of involvement in rats with PNS myelin-induced or P2-induced acute EAN [4,5]. Electrophysiological studies in animals with acute EAN have demonstrated conduction abnormalities in the PNS [6-14], but have not assessed whether focal conduction block occurs in the dorsal root ganglion. We have previously demonstrated focal conduction block in the dorsal root ganglia of rabbits and, to a lesser extent, in rats with acute experimental allergic encephalomyelitis, an autoimmune demyelinating disease that affects the central nervous system and also results in PNS lesions similar to those of EAN [15-18]. The present study was undertaken to determine whether similar focal conduction block occurs in the dorsal root ganglion in rats with EAN.

Materials and Methods

Induction of EAN

Female Lewis rats (JC strain) bred by the Central Animal Breeding House of the University of Queensland (Brisbane, Australia) were used. Rats aged 7 to 10 weeks were inoculated with a total of 0.1 ml of emulsion (containing 2 mg of bovine intradural root myelin, 0.05 ml of complete Freund's adjuvant (Difco, Detroit, MI), an additional 0.5 *mg Mycobacterium tuberculosis* H37RA (Difco), and 0.05 ml of saline) per rat. The inoculum was given in divided doses into the medial footpad of each hindlimb. The myelin was prepared by sucrose density gradient centrifugation from bovine intradural roots obtained within 1 hour of death and dissected immediately. The rats were examined daily from 7 days after inoculation.

Controls

Normal female Lewis rats, 9 to 12 weeks old, served as controls for the electrophysiological studies. As these studies were performed on the rats with EAN about 2 weeks after inoculation, the control rats were the same age as the rats with EAN at the time of the studies.

Electrophysiological Studies

Anesthesia was induced by the intraperitoneal injection of ketamine hydrochloride (74 mg/kg), xylazine (9 mg/kg), and atropine (36 µg/kg), and maintained with further intraperitoneal injections of one-half these doses. An adequate depth of anesthesia was maintained without depressing the corneal reflex. The rats breathed spontaneously through a tracheal cannula. Hartmann's solution (8 ml) (compound sodium lactate BP, Baxter Health Care, Old Toongabbie, New South Wales, Australia) was given intraperitoneally at the beginning of each experiment, and 1 ml of Haemaccel (polygeline, Hoechst, Melbourne, Australia) was given intraperitoneally after the laminectomy had been performed.

A T12-L6 laminectomy was performed and the left L-4 dorsal root ganglion and spinal nerve were exposed. The rat was mounted in an animal frame, and a metal box, through which water at 37°C was circulated, was placed under the rat. A pool was made with the skin flaps and the dura was opened. After the left hindlimb had been extended and sup-ported in a horizontal position, the left sciatic nerve was exposed in the posterior thigh and a skin pool formed. The sciatic nerve in the mid-thigh was dissected free with care to avoid damage to its blood supply. After the exposed nervous tissues had been rinsed in Hartmann's solution, paraffin oil was added to cover the tissues. A controlled radiant heat lamp maintained the laminectomy and sciatic pools at 37°C.

M-Wave and H-Reflex Recordings

The freed sciatic nerve was lifted away from the volume conductor and stimulated in continuity with platinum electrodes, 3 mm apart (cathode distal), delivering 0.1 msec square-wave voltage pulses at 1 Hz. Recordings were made with 25-gauge needle electrodes, one in the belly of the fourth dorsal interosseus muscle and the other subcutaneously in the plantar aspect of the distal fourth digit of the left hindfoot. As the amplitude of the normal H reflex was greater after a period of no stimulation for several seconds, the maximal H reflex was usually recorded as the response to the first stimulus after a 5-second period of no stimulation. For all recordings in the present study, short leads connected the recording electrodes to field-effect-transistor source-followers, thence to a preamplifier (bandwidth limited to 5.3–10,000 Hz), and thence for display on an oscilloscope. Negativity at the active electrode gave an upward deflection on the oscilloscope. Oscilloscope traces were photographed for measurement.

Spinal Nerve, Dorsal Root Ganglion, and Dorsal Root Entry Zone Recordings

The left sciatic nerve was stimulated in continuity with 0.1-msec pulses delivered at 1 Hz as described above, except that the polarity of the stimulating electrodes was reversed. Volume conductor recordings were made, in turn, over the left L-4 spinal nerve (3 mm distal to the midpoint of the dorsal root ganglion), dorsal root ganglion, and dorsal root entry zone with a 0.5-mm-diameter silver ball electrode as the active electrode. The reference electrode was a platinum wire placed in the right paravertebral region at the same level. Conduction velocities were calculated after allowing for a utilization time of 0.1 msec [19].

Monophasic Dorsal Root Recordings

After the above recordings had been made, the left L-4 dorsal root was cut between two ties close to the dorsal root entry zone. The distal cut end was lifted away from the volume conductor into oil and placed on a pair of platinum wire hook electrodes 3 mm apart. The left sciatic nerve was stimulated in continuity as for the spinal nerve, dorsal root ganglion, and dorsal root entry zone recordings. The area under the curve of the compound action potential was derived by tracing the photographed curve on a digitizer tablet linked to a micro-computer.

At the end of the experiment, the dissection was extended to expose the entire length of the conduction pathway from the sciatic nerve to the relevant recording sites. Conduction distance was measured as the length of a thread placed along the conduction pathway.

Statistical Analysis

Student's *t* test was used for statistical analysis.

Histological Studies

At the end of the electrophysiological studies, 2 of the rats with EAN were perfused through the left ventricle with 0.9% saline followed by 2.5% glutaraldehyde/2% formaldehyde in 0.1 M sodium cacodylate buffer (pH 7.3-7.4). The left sciatic nerve and the left L-4 proximal spinal nerve, dorsal root ganglion, and dorsal root were removed and immersed in fixative. The tissues were postfixed with 1% osmium tetroxide, embedded in Epox 812 (Ernest F. Fullam, Schenec-

tady, NY), sectioned (1 μm), and stained with toluidine blue for light microscopy.

Results

Clinical Findings

Neurological signs commenced 9 to 12 days after inoculation and progressed over the next 2 to 3 days. Electrophysiological studies were performed 12 to 15 days after inoculation (2-4 days after the onset of neurological signs), at which stage the rats had tail paralysis, and hindlimb and forelimb ataxia and weakness. The ataxia was manifested by abnormalities of limb placement and by ataxia of gait.

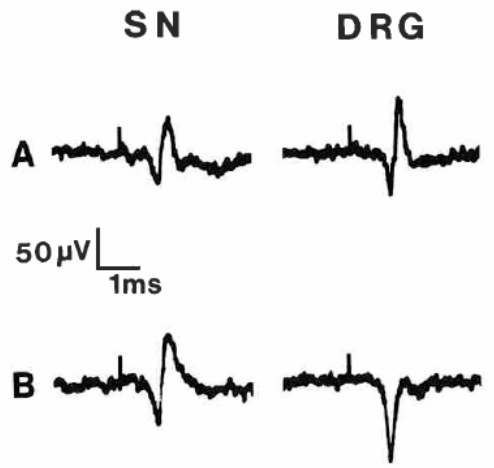

Fig 1. Volume conductor recordings of the maximal L-4 spinal nerve (SN) and dorsal root ganglion (DRG) responses evoked by sciatic nerve stimulation in a normal control rat (A) and in a rat with EAN (B). in these and all subsequent recordings, the onset of the stimulus is indicated by a vertical line.

Spinal Nerve Recordings

In normal control rats, the volume conductor recording of the maximal L-4 spinal nerve response evoked by sciatic nerve stimulation consisted of an initially positive biphasic wave (Fig 1). The positivity is due to passive outward current driven by the approaching impulses, and the negativity is due to active inward current occurring during the rising phase of the action potential under the active recording electrode. The ratio of the amplitude of the negativity to that of the positivity is equal to or greater than 1.0. In the absence of temporal dispersion, this amplitude ratio serves as a reliable index of conduction block at the recording site, the ratio progressively falling with higher proportions of fibers undergoing block [16, 20]. In rats with EAN, the mean values for the peak-to peak amplitude, amplitude ratio, and conduction velocity of the peak of the negativity did not differ significantly from those in the normal controls (Table 1; see Fig 1). These findings indicate essentially normal conduction between the sciatic nerve and proximal spinal nerve in rats with EAN. In 2 of these rats with EAN, however, the amplitude ratios were less than 1.0 (0.8 and 0.7), suggesting conduction block in some fibers in the proximal spinal nerve. The conduction velocities were also low in these 2 rats (37.1 m/sec).

Table 1. L-4 Spinal Nerve Recordings in Rats with EAN

	Controls[a] (n=4)	EAN[a] (n=6)	*p*
Peak-to-peak amplitude (μV)	96 ± 35	91 ± 17	NS
Ratio of amplitude of negativity to amplitude of positivity	1.2 ± 0.2	1.1 ± 0.3	NS
Conduction velocity of peak of negativity (m/sec)	50.0 ± 1.4	44.4 ± 6.5	NS

[a]Mean ± SD obtained from recordings of maximal L-4 spinal nerve response.
EAN = experimental allergic neuritis; NS = not significant ($p > 0.05$).

Table 2. L-4 Dorsal Root Ganglion Recordings in Rats with EAN

	Controls[a] (n=4)	EAN[a] (n=6)	*p*
Peak-to-peak amplitude (μV)	155 ± 78	73 ± 19	< 0.05
Ratio of amplitude of negativity to amplitude of positivity	1.1 ± 0.1	0.2 ± 0.2	< 0.001
Conduction velocity of peak of negativity (m/sec)	46.1 ± 2.7	40.1 ± 5.9 (n=4)[b]	NS

[a]Mean ± SD obtained from recordings of maximal L-4 dorsal root ganglion response.
[b]Negativity absent in 2 rats with EAN.
EAN = experimental allergic neuritis; NS = not significant ($p > 0.05$).

Dorsal Root Ganglion Recordings

In the normal control rat, the volume conductor recording of the L-4 dorsal root ganglion response evoked by sciatic nerve stimulation was similar in configuration to that of the L-4 spinal nerve response (see Fig 1). The amplitude ratio was equal to or greater than 1.0. In rats with EAN, the mean peak-to-peak amplitude of the maximal L-4 dorsal root ganglion response was moderately reduced, and the mean amplitude ratio was markedly reduced compared with those of the normal controls (Table 2; see Fig 1). The pronounced reduction in the amplitude ratio (without temporal dispersion) indicates conduction block in a high proportion of the large-diameter afferent fibers in the dorsal root ganglion. The mean conduction velocity of the peak of the negativity in those rats with EAN in which negativity could still be recorded was lower than that of the normal controls, but the difference was not statistically significant (see Table 2).

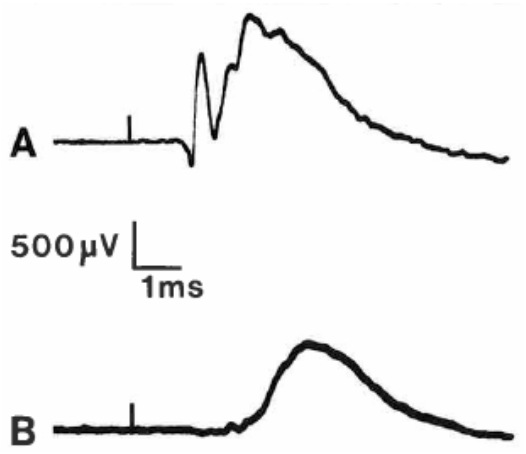

Fig 2. Volume conductor recordings of the L-4 dorsal root entry zone afferent volley potential and N wave evoked by stimulation of the sciatic nerve at the intensity giving the maximal N wave (supramaximal for afferent volley) in a normal control rat (A) and in a rat with EAN (B).

Dorsal Root Entry Zone Recordings

To assess sensory conduction along the whole length of the peripheral pathway from the sciatic nerve to the lumbar dorsal root entry zone, volume conductor recordings were made of the L-4 dorsal root entry zone response evoked by sciatic nerve stimulation. In normal control rats, the response consists of an initial biphasic wave, representing the afferent volley, followed by a late slow negative wave, the N wave (Fig 2). The N wave is a field potential due to synaptic currents in the second-order dorsal horn neurons excited mainly by low-threshold cutaneous afferents. In rats with EAN, the mean peak-to-peak amplitude of the maximal afferent volley potential was severely reduced compared with that of normal controls (Table 3; see Fig 2). In the absence of temporal dispersion, this indicates conduction failure in a high proportion of the large-diameter afferents between the sciatic nerve and the dorsal root entry zone. As the L-4 spinal nerve responses were virtually normal, the conduction failure is not due to a failure of excitation, but conduction block. The demonstrated conduction block in the dorsal root

ganglion largely explains this, but it is likely that conduction block may be occurring in the dorsal root in some fibers that were able to transmit signals through the dorsal root ganglion. The mean conduction velocity of the peak of the negativity of the afferent volley potential was reduced compared with that of the normal controls due to conduction block, slowing of the fastest fibers, or both (see Table 3). In rats with EAN, the mean latency to the peak of the maximal N wave was significantly prolonged (see Table 3). The mean amplitude of the peak of the maximal N wave was reduced, but the difference was not significant.

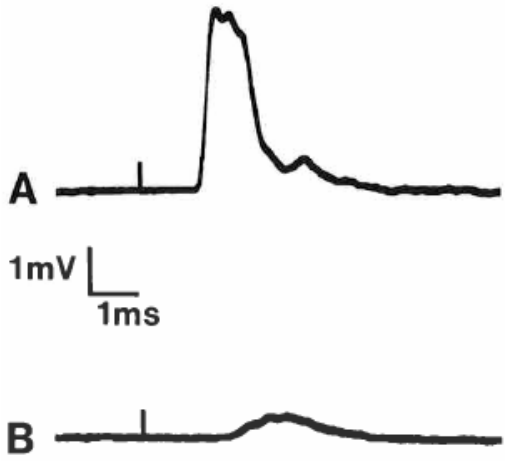

Fig 3. Monophasic recordings of the maximal L-4 dorsal root response evoked by stimulation of the sciatic nerve in a normal control rat (A) and in a rat with EAN (B).

Monophasic Dorsal Root Recordings

A monophasic recording of the maximal response evoked from the distal cut end of the L-4 dorsal root when the sciatic nerve was stimulated is shown in Figure 3. The mean values of the peak amplitude and of the area under the curve were significantly reduced in rats with EAN (Table 4; see Fig 3). These observations confirm the finding of conduction block in a high pro-portion of the large-diameter afferent fibers. The mean velocities of the onset and peak of the response were significantly reduced, indicating conduction block, slowing of the fastest fibers, or both (see Table 4).

Table 3. L-4 Dorsal Root Entry Zone Recordings in Rats with EAN

	Controls[a] (n = 17)	EAN[a] (n = 4)	*p*
Afferent volley potential			
Peak-to-peak amplitude (μV)	1,215 ± 276	63 ± 20	< 0.001
Conduction velocity of peak of negativity (m/sec)	55.6 ± 4.8	37.8 ± 3.4	< 0.001
N wave			
Peak amplitude (μV)	1,331 ± 294	970 ± 396	NS
Latency to peak (msec)	2.4 ± 0.2	4.0 ± 0.3	< 0.001

[a]Mean ± SD obtained from recordings of maximal afferent volley potential and maximal N wave.
EAN = experimental allergic neuritis; NS = not significant ($p > 0.05$).

M-Wave and H-Reflex Recordings

In rats with EAN, the mean peak-to-peak amplitude of the maximal M wave evoked in the fourth dorsal interosseus muscle by sciatic nerve stimulation was not significantly different from that of normal controls (Table 5; Fig 4). The mean latency to the onset of the M wave, however, was significantly prolonged. In normal rats, the mean ratio of the amplitude of the maximal H reflex to the amplitude of the maximal M wave was 0.46 ± 0.05. In all rats with EAN, the H reflex was absent.

Histological Findings

Histological studies were performed on 2 of the rats with EAN after the electrophysiological studies. The findings were similar to those we have previously de-scribed in this model [5]. In each rat, there was prominent primary demyelination, mononuclear cell infiltration, and myelin debris within macrophages in the left L-4 dorsal root ganglion, which was a site of conduction block (Fig 5). Inflammation and demyelination were also present in the respective dorsal roots. The left L-4 proximal spinal nerve was normal in 1 rat but showed mild inflammation and demyelination in the other rat, which had had a low spinal nerve amplitude ratio and conduction velocity. The sciatic nerve sections were normal in both rats.

Table 4. Monophasic L-4 Dorsal Root Recordings in Rats with EAN

	Controls[a] (n = 3)	EAN[a] (n = 5)	*p*
Peak amplitude (mV)	3.18 ± 0.56	0.45 ± 0.13	< 0.001
Area under curve (mVmsec)	3.22 ± 0.55	0.51 ± 0.11	< 0.001
Conduction velocity of onset (m/sec)	74.2 ± 3.8	51.2 ± 9.2	< 0.01
Conduction velocity of peak (m/sec)	46.4 ± 1.4	31.7 ± 5.1	< 0.005

[a]Mean ± SD obtained from recordings of maximal L-4 dorsal root response.
EAN = experimental allergic neuritis.

Discussion

The major new finding of the present study is focal conduction block in a high proportion of large-diameter afferent fibers in the dorsal root ganglion in Lewis rats with acute EAN. In contrast, nerve conduction in the peripheral nerve and spinal nerve was essentially normal apart from probable conduction block in some fibers in the proximal spinal nerve in a minority of rats. The electrophysiological findings accord well with the histological findings of prominent inflammation and demyelination in the dorsal root ganglion, with minimal involvement of the proximal spinal nerve and no involvement of the sciatic nerve. The conduction block in the dorsal root ganglion is readily explained by this demyelination. As demyelination is also present in the dorsal roots in this model, it is likely that conduction block occurs in the dorsal root in fibers that are able to transmit signals through the ganglion. Conduction block in the dorsal root ganglion and probably in the dorsal root explains the severely reduced afferent volley arriving at the dorsal root entry zone of the spinal cord. The resultant functional deafferentation explains the clinical finding of hindlimb ataxia. It is likely that the tail paralysis and limb weakness in these rats are due to demyelination-induced nerve conduction block in the ventral roots, but electrophysiological studies were not performed on the ventral roots in the present study.

Table 5. M Wave and H Reflex in Rats with EAN

	Controls[a] (n = 9)	EAN[a] (n = 6)	*p*
Peak-to-peak amplitude of M wave (mV)	4.8 ± 0.8	5.9 ± 2.5	NS
Latency to onset of M wave (msec)	2.5 ± 0.2	3.1 ± 0.3	< 0.005
Ratio of peak-to-peak amplitude of H reflex to peak-to-peak amplitude of M wave	0.46 ± 0.05	0.0 ± 0.0	< 0.001

[a] Mean ± SD obtained from recordings of maximal M wave and maximal H reflex in fourth dorsal interosseus muscle.
EAN = experimental allergic neuritis; NS = not significant ($p > 0.05$).

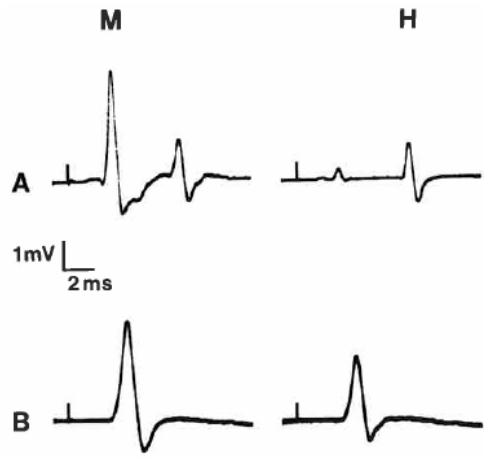

Fig 4. *Maximal M wave (M) and maximal H reflex (H) evoked in the fourth dorsal interosseus muscle by sciatic nerve stimulation in a normal control rat (A) and in a rat with EAN (B).*

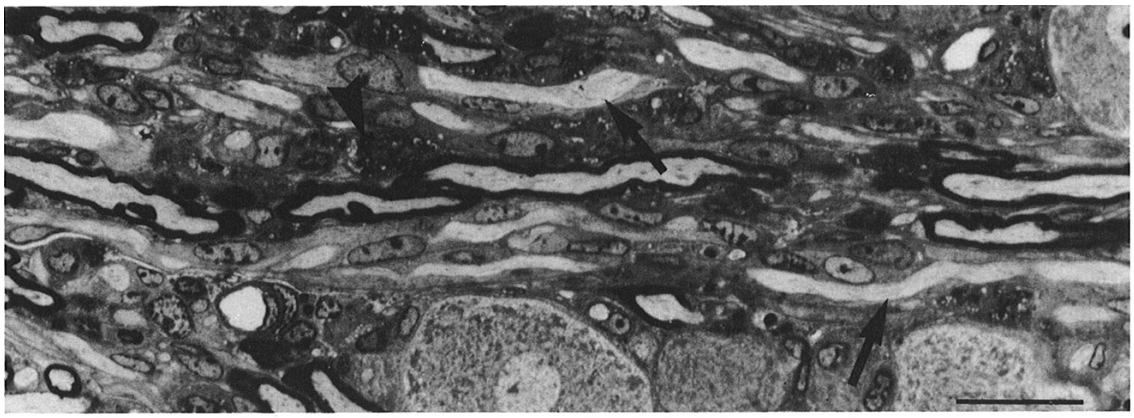

Fig 5. *Longitudinal section through the L-4 dorsal root ganglion of a rat with EAN in which conduction block was demonstrated. Demyelinated axons* (arrows) *and intracellular myelin debris* (arrowhead) *can be seen. Epoxy section stained with toluidine blue. Scale bar = 25 µm.*

A striking finding in the present study was the relative preservation of the N-wave amplitude despite conduction block in a high proportion of the large-diameter afferents and severe reduction of the afferent volley potential at the dorsal root entry zone. This illustrates the unreliability of the amplitude of postsynaptic field potentials as an index of conduction block in presynaptic axons. In contrast to the relatively minor change in the N-wave amplitude, there was a prominent prolongation of the latency to the peak of the N wave. This prolongation of N-wave latency serves as a sensitive indicator of conduction block in the afferent pathway, as we have previously shown [16].

In the present study, the M wave evoked in the fourth dorsal interosseus muscle by sciatic nerve stimulation in the thigh was normal in amplitude and con-figuration in rats with EAN, yet the latency was prolonged. The cause of the latency prolongation is unclear but it may reflect slowing due to demyelination of the intramuscular nerve twigs. The H reflex was absent in all rats with EAN. In the Lewis rat, the H reflex of the fourth dorsal interosseus muscle is mediated through the L-5 dorsal and ventral roots and, to a lesser extent, the L-6 ventral root [20]. The absent H reflex is most likely due to demyelination-induced conduction block in the relevant dorsal root ganglion and dorsal root and ventral roots.

The conduction block in the dorsal root ganglion in rats with acute EAN is similar to that we have previously described in rabbits with acute experimental allergic encephalomyelitis (EAE) induced by inoculation with whole spinal cord [15-17] and similar to that in cats with diphtheritic neuropathy [21]. We have also observed conduction block, although to a lesser degree, in the dorsal root ganglion in rats with acute EAE induced by inoculation with whole spinal cord [18]. Prominent conduction

abnormalities due to demyelination of the dorsal root ganglion and dorsal root have also been demonstrated in Lewis rats with chronic re-lapsing EAE [22].

The selective involvement of the dorsal root ganglion in rats with acute EAN may be explained by the deficient blood-nerve barrier of the dorsal root ganglion [23], which may facilitate access of circulating lymphocytes and humoral factors, including antibody and complement, into the ganglion. A similar vulnerability of the rabbit dorsal root ganglion [24] explains the selective involvement of the dorsal root ganglion in rabbits with EAN and EAE [1, 3, 16, 17). Although the dorsal root ganglion is a site of predilection for the lesions of EAN, peripheral nerve involvement increases and may become extensive when the amount of myelin in the inoculum is increased [25]. Although the inoculum used in the present study contained 2 mg of myelin, the histological findings resemble those observed when a dose of 0.5 mg of myelin was used by Hahn and colleagues [25]. Axonal degeneration also increases with increasing myelin in the inoculum [25]. Furthermore, spinal nerve involvement increases during relapses of EAN [5]. In contrast to the situation in the rabbit and the rat, the peripheral nerve is a site of predilection for the lesions of EAN in the guinea-pig [3], owing to the deficiency of the blood-nerve barrier in the peripheral nerve of that species [24).

In conclusion, we have demonstrated focal conduction block due to demyelination of the dorsal root ganglion in acute EAN in the rat. This vulnerability of the dorsal root ganglion may have implications for the inflammatory demyelinating diseases of the human PNS.

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