Nature (1982) 296(5860):860-862.

Conduction Block In The Peripheral Nervous System In Experimental Allergic Encephalomyelitis

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Abstract

Experimental allergic encephalomyelitis (EAE) has been widely studied as a model of multiple sclerosis, a central nervous system (CNS) disease of unknown aetiology. The clinical features of both EAE and multiple sclerosis provide the only guide to the progress and severity of these diseases, and are used to assess the response to treatment. In such comparisons the clinical features of EAE are assumed to be due to lesions in the CNS, but in this disease there is also histological evidence of damage to the peripheral nervous system". However, the functional consequences of such peripheral lesions have been entirely ignored. To examine this we have studied nerve conduction in rabbits with EAE. We report here that most of the large diameter afferent fibres are blocked in the region of the dorsal root ganglion and at the dorsal root entry zone, thus accounting for the loss of tendon jerks and also, through the severe loss of proprioceptive information, the ataxia of these animals. We conclude that whenever clinical comparisons are made between EAE and multiple sclerosis, the pathophysiology associated with the histological damage of the peripheral nervous system must be taken into account.

EAE is a disease induced by inoculating with CNS-derived antigens and adjuvants, and is characterized clinically by limb ataxia and weakness[9] and histologically by CNS lesions consisting of meningeal infiltration with mononuclear cells, perivascular cuffing and para-adventitial infiltration with mononuclear cells and perivascular demyelination[9,10] This disease has been studied extensively, especially recently in its chronic relapsing form", because it is widely accepted as an animal model of multiple sclerosis[12]. However, it has been assumed that the clinical features of EAE are due to CNS lesions even though histological damage of the peripheral nervous system occurs in many species such as the rabbit[3,4], mouse[5], guinea pig[1,5] and monkey[2] and when antigens derived solely from the CNS are used[3]. It also occurs in rabbits with chronic EAE[6], and in guinea pigs[7] and rats[8] with chronic relapsing EAE. Thus, it is possible that the clinical features of EAE are due to lesions of the peripheral rather than the central nervous system. This question needs resolving because the improvement or suppression of the clinical features of EAE by agents such as myelin basic protein[13] and immunosuppressants[14] provides the basis for their use in the treatment of multiple sclerosis.

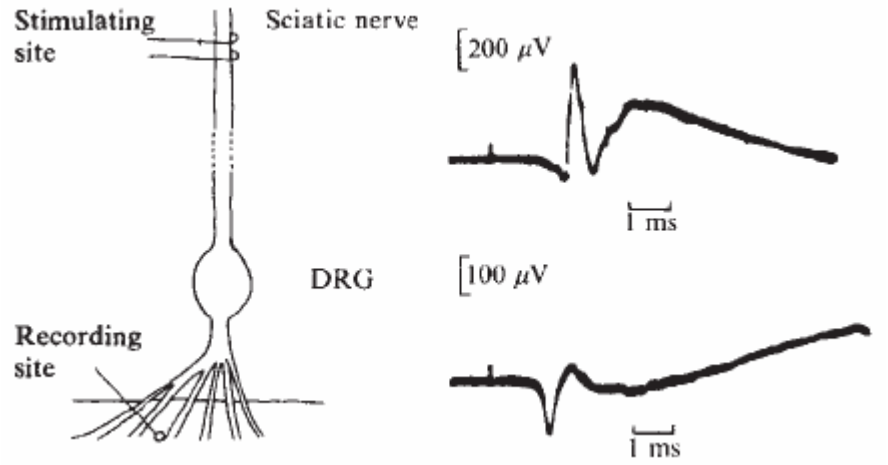

Fig. 1 Recording in the volume conductor over the S1 dorsal root entry zone in response to sciatic nerve stimulation. In each trace, positivity at the active electrode gives a downward deflection. Upper trace, normal rabbit; lower trace, rabbit with EAE. Note the difference in gain. DRG, dorsal root ganglion.

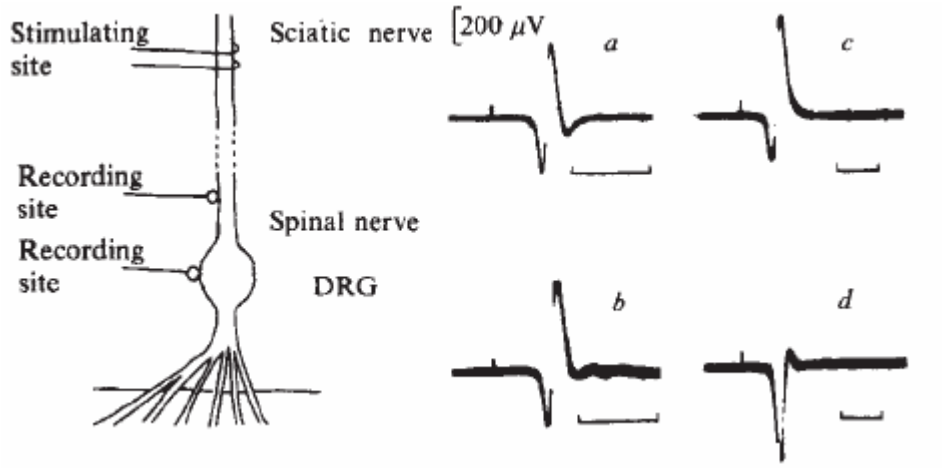

Fig. 2 Recordings in the volume conductor over the spinal nerve and the DRG in response to sciatic nerve stimulation. *a*, Recording over Si spinal nerve in normal rabbit. *b*, Recording over normal Sl DRG. *c*, Recording over Si spinal nerve of rabbit with EAE. *d*, Recording over Sl DRG from the same rabbit with EAE. Time bars, 2 ms.

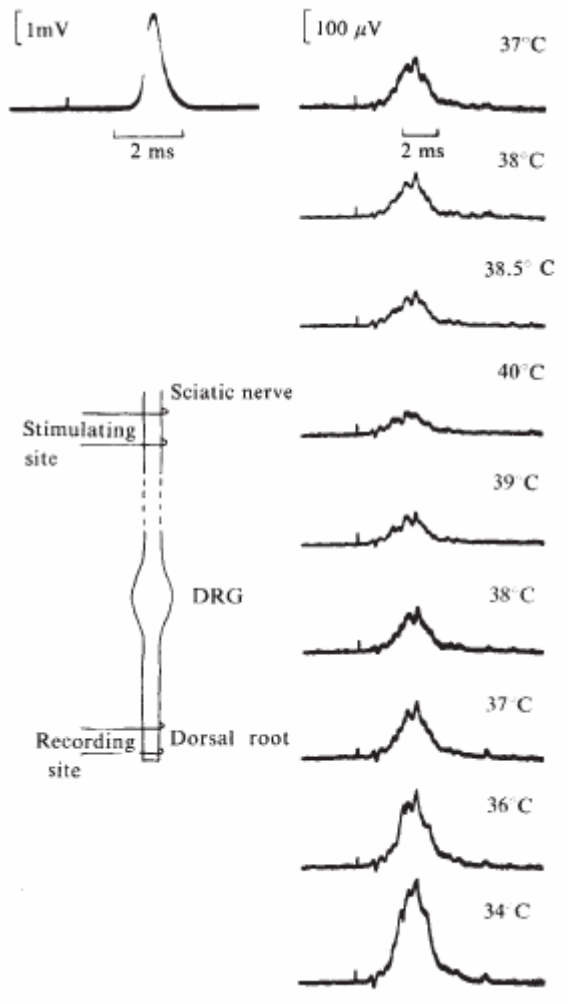

Fig. 3 Monophasic recording from the distal cut end of S1 dorsal root in response to sciatic nerve stimulation. Upper left trace, normal rabbit. Traces on the right are recordings from a rabbit with EAE at various laminectomy pool temperatures, as indicated on the right. Note the difference in gain and time base.

We have therefore made a clinical, physiological and histological study of EAE in New Zealand white rabbits inoculated intradermally with homogenized rabbit spinal cord and complete Freund's

adjuvant. The clinical onset occurred 15-23 days after inoculation and was typical of that previously described[9], with weight loss, ataxia and weakness of the limbs occurring over 3-4 days. We also examined the tendon jerks and found that these usually disappeared about 2 days after the clinical onset, indicating a lesion interrupting the monosynaptic reflex arc. All the clinical findings could thus be accounted for by lesions in the peripheral nervous system. Histological examination revealed typical, widespread CNS lesions as well as lesions in the dorsal root ganglia and dorsal and ventral roots.

In terminal experiments, 2-6 days after clinical onset, animals were anaesthetized intravenously with 25% urethane, a lumbosacral laminectomy was performed and the left sciatic nerve was exposed in the posterior thigh. The left medial gastrocnemius compound muscle action potential elicited by stimulation of the sciatic nerve in the mid-thigh was normal in all of 12 animals studied.

Conduction into the roots and spinal cord was studied in 10 affected animals. Figure 1 shows typical responses recorded in the volume conductor over the left S1 dorsal root entry zone in response to sciatic nerve stimulation. The upper trace (from a normal control animal) shows a triphasic (positive-negative-positive) wave representing the afferent volley, followed by a longer latency, slow negative wave, the N wave. The initial positive wave is due to the passive outward currents driven by the last activated nodes of Ranvier; the negative phase of the afferent volley is due to the active inward currents occurring during the rising phase of the action potentials and ranges from 300 to 800 μV in amplitude. The peak-to-peak amplitude of the triphasic wave ranges from 400 to 1,000 μV. The N wave is due to the synaptic currents in the second order dorsal horn neurones excited mainly by low threshold cutaneous afferents.

The lower trace in Fig. 1 (from an affected animal) shows three characteristic abnormalities. (1) A very reduced peak-to-peak amplitude (usually <200 μV) indicating that only a small proportion of the large diameter afferent fibres are conducting past the dorsal root ganglion to this point. (2) A very reduced (usually <50 μV) negative wave and a relative increase in the positive wave of the afferent volley, indicating that most of the large diameter fibres still conducting past the ganglion are blocking in the vicinity of the dorsal root entry zone. (3) A delayed peak of the N wave possibly due to conduction persisting in small fibres.

To determine the site of conduction block, volume conductor recordings were made over the spinal nerve and dorsal root ganglion (Fig. 2); traces *a* and *b* are the responses over the normal S1 spinal nerve and S1 dorsal root ganglion, respectively. They are similar and consist of an initial positive wave followed by a larger negative wave. Figure 2c shows a recording over the S1 spinal nerve of a rabbit with EAE and is normal. The recording in Fig. 2d was obtained over the S1 dorsal root ganglion of the same affected animal and shows a large positive wave followed by a small negative wave, indicating that most of the fibres are blocking at this point.

To investigate the nature of the conduction block, the effects of temperature were studied. Recently, it has been shown[15,16] that in demyelinated single fibres, increasing the temperature within the physiological range produces reversible conduction block, and that in some fibres conduction block can be overcome by reducing the temperature by as little as 0.5°C. The method used to study the effects of temperature is shown diagrammatically in Fig. 3. The distal cut end of the S1 dorsal root was placed on a pair of electrodes and a monophasic recording made of the compound action potential in response to sciatic nerve stimulation. The upper left trace is from a normal anaesthetized rabbit. The right-hand traces were made at various temperatures of the laminectomy oil pool of a rabbit on the fifth day of clinical disease. On the previous day we increased the body temperature of this animal by 1.5°C- this caused a reversible increase in ataxia. The response at 37°C was greatly reduced in amplitude (note the difference in gain) with an area less than 30% of the normal compound action potential, suggesting that most of the large diameter fibres were blocking in the region of the dorsal root ganglion. The area of the response was progressively reduced as the temperature was increased to 40°C, which indicates that block was occurring in an increasing number of fibres. When the temperature was reduced to 37°C, the response regained its original area. On further cooling to 34°C the area increased by 100%, showing that conduction was restored in a significant number of fibres. These findings strongly suggest that the conduction block is due to demyelination.

From our studies we conclude that the loss of tendon jerks and the ataxia of rabbits with EAE can be accounted for by conduction block in most of the large diameter afferent fibres in the region of the dorsal root ganglion and dorsal root entry zone. Such conduction block would mask the clinical expression of any central lesions which alone could produce ataxia. Clearly, these functional considerations must be taken into account when making a clinical comparison between EAE and multiple sclerosis.

Acknowledgments

We thank Drs L. Cuzner and C. Bolton for advice concerning the inoculation procedure. Support from the National Fund for Research into Crippling Diseases and the Brain Research Trust is gratefully acknowledged.

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